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\*Rubin, M. I., in: Mitchell-Nelson Textbook of Pediatrics, 4th ed., p. 1261, Saunders 1943

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Executive Office  
423 La Salle Medical Bldg.  
Minneapolis 2, Minnesota

Annals of Allergy is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, editorials, case reports, new suggestions, news items and matters concerning the affairs of the American College of Allergists.

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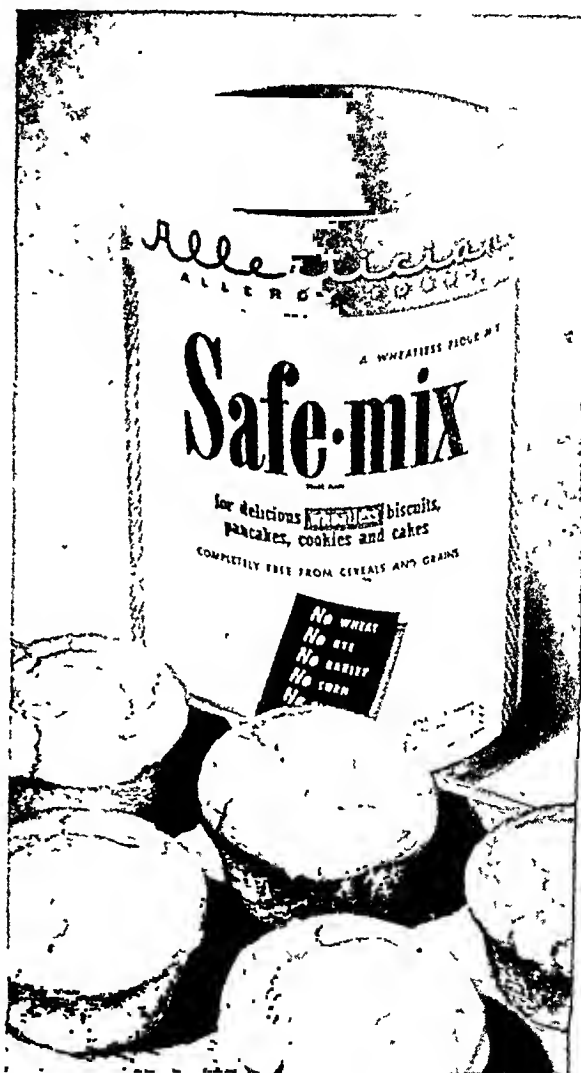
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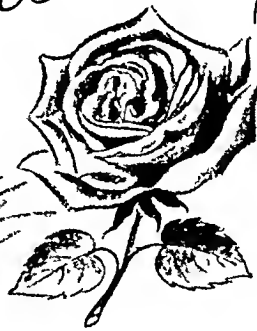
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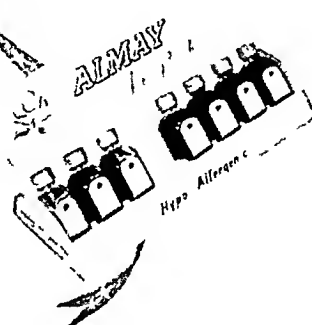
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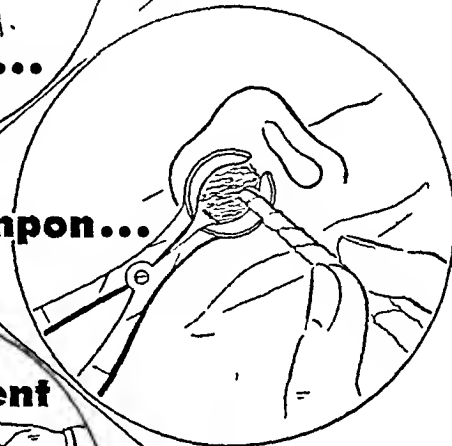
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Volume 6

November-December, 1948

Number 6

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## MANAGEMENT OF THE PRE-ALLERGIC CHILD

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I HAVE been asked to discuss the problem of the pre-allergic child. Does this mean the child who presents manifestations resembling but not clearly defined as allergic? Or, should one regard every child as potentially capable of developing allergy and consider that the management of the pre-allergic child encompasses the whole problem of the prevention of allergy? I believe the latter is indicated, and shall proceed from that standpoint.

The evidence presented in the literature shows that the placenta, the intestinal tract and the respiratory tract are permeable to unchanged or whole native proteins. Unaltered allergens may, therefore, enter the blood stream via these portals. Following the entrance of these antigens, allergic antibodies are formed and become fixed to the smooth muscle cells. When the antigen repeatedly enters the body, the child then begins to manifest true allergic episodes, either in the form of urticaria, eczema, hay fever, asthma, gastrointestinal symptoms, migraine or other neuropathies. With this brief sketch in mind, it would seem that the pre-allergic phase may be the interval which elapses before the readily recognizable patterns are established after the antigen has gained entrance into the body through the natural portals of the placenta, intestinal wall or respiratory tract, or by artificial means through injections, topical application via a break in the skin, or as a result of insect or animal bites.

The organism is provided with certain barriers which prevent the invasion of allergens into the blood stream. These barriers are the relatively impermeable skin and the mucous membranes covering the outer surfaces and body cavities and their respective tissue juices. Finally, such foreign proteins may be excreted from the body in their

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Presented at the Fall Graduate Instructional Course in Allergy, The American College of Allergists, under the auspices of the College of Medicine, University of Cincinnati, Cincinnati, Ohio, November 8, 1947.

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original state via the kidney. These barriers are not equally effective in all individuals, nor are they effective to a like extent at all times in the same individual, for the immaturity of the organism, pathologic states and disturbed physiology may alter them. Therefore, while individuals may be similarly exposed to antigens, it does not follow that these antigens will be similarly disposed of by the body. The alteration of any of the barriers may permit the foreign protein to enter the blood stream directly and generate specific sensitizing antibodies. Yet another factor of significance is the individual difference in capacity to form antibodies.

It may be hypothesized, therefore, that man battles continually against the invasion of foreign proteins. The difference between the normal individual, who battles successfully, and the allergic, who does not, may more largely be concerned with quantitative rather than with qualitative considerations. We must assume that quantitative applies not solely to the amount to which the individual is exposed, but to the amount of antigen which actually penetrates the tissue cells.

In the management of childhood, therefore, from the standpoint of prophylaxis, we should adopt measures aiming at the reduction of undue exposure to highly antigenic substances, particularly in vulnerable periods—roughly, intra-uterine life, infancy, illness and convalescence.

#### FOOD SENSITIVITY

*Congenital Allergy or Intra-uterine Sensitization.*—The cravings of the parturient mother and her excessive indulgence in certain foods during pregnancy account in part for some cases of food sensitivity in infancy, which to all appearances occur spontaneously from the ingestion of a new food.<sup>5</sup> If the mother herself is sensitive to a food, she may sensitize the infant passively to the particular allergen.

The pregnant woman, therefore, should be advised against over-indulgence of any food cravings. At times, this excessive intake of a particular food may escape detection. For example, a patient may deny eating eggs in excess, and yet a careful inquiry will disclose that she is having them in the form of mayonnaise—on sandwiches and in salads—in eggnogs or other beverages, in cakes, icings, puddings, ice cream and other prepared foods. The same will hold true for milk, nuts, grains and other products which enter largely into the preparation of foods. Excessive cravings for fish, spices, nuts, fruits and vegetables are more apparent. Episodic indulgences may be as frequent a cause. A food debauch, particularly in the latter months of pregnancy, may induce sensitization in the offspring. Fad diets may have the same tendency.

A widely varied diet is helpful in meeting the problem. If the nutritional requirements of the pregnant woman make it imperative for her to have larger than usual quantities of any food element, the obstetrician may prescribe them in part in "allergenically denatured" form.

Investigations of various forms of heat-treated milks, malt and corn

sugars, cereal grains and breadstuffs by Ratner and Gruel<sup>6</sup> demonstrated that animals, which had been rendered hypersensitive to certain specific food substances, can tolerate certain forms of heat-treated homologous products with little or no reaction. The studies on milk showed that the lactalbumin and lactoglobulin fractions were reduced in antigenicity when heated, i. e., evaporated or boiled. The casein is unaffected. Malt extracts, on the other hand, were highly allergenic even if heated, whereas dextri-maltose was not. With the grain foods, we found that not until the specific foods were tested could it be determined which were "allergenically denatured" and which were not. For example, certain commercially prepared dry cereals appear to be denatured, whereas certain home cooked cereals, breads and crackers are not.

From the work of Chick and Martin<sup>7</sup> we learn that egg white is reduced in antigenicity when heated in water, and, from clinical experience that hard boiled eggs can be tolerated by the individual who is sensitive to the albumen fraction.

Yet, foods such as nuts and fish remain highly antigenic even after cooking.

The cardinal principles to be borne in mind in avoiding intra-uterine food sensitization would be: (1) prescribe a widely varied diet, (2) give a portion of the food in "allergenically denatured" form, (3) discourage overeating, (4) warn against excessive indulgence in any single protein food and satisfaction of food cravings.

*Sensitization in the Neonatal Period.*—A newborn infant who receives one or several relief bottles of raw or dry milk during the first two weeks, and who then is put back on the breast entirely, may develop milk sensitization which is not evidenced until weaning is attempted. The interval between the first relief bottles and the beginning of weaning serves as the incubation period. This preliminary contact with cow's milk permits sensitization to become established. Such a situation duplicates the conditions of animal experimentation.

Sensitization may be prevented by prescribing some form of allergenicallly denatured milk for the relief formula, in conjunction with some denatured form of carbohydrate such as dextri-maltose.

*Sensitization Following Severe Gastrointestinal Disturbances.*—Hutinel<sup>2</sup> and others observed that after severe gastrointestinal disturbances the child may manifest sensitivity to a food for which he had complete tolerance prior to his illness. The explanation lies in the fact that the increased permeability of the intestinal wall engendered by diarrhea, for example, permits the ready entrance of unchanged protein into the blood stream.

It is important, therefore, during treatment and convalescent care of severe intestinal disturbances, such as diarrhea, dysentery, and typhoid

fever, (1) to give "allergenicly denatured" foods, (2) to give a varied diet, and (3) to avoid new foods and raw or lightly cooked foods.

*Sensitization During Convalescence from Disease.*—The increased permeability of the intestinal wall, characteristic of severe intestinal disturbances, also occurs during convalescence from other diseases, and following surgical operations, where loss of weight and wasting are evident. Foods that are not cooked, for example, eggnogs, fruit whips and raw milk, are all potential sensitizing agents. From what has been pointed out, the wise course to follow is the same as that indicated in intestinal cases, rather than the generally prescribed diet which at present consists largely of raw and lightly cooked foods.

*Sensitization Resulting from Excesses in Diet and Unusual Foods.*—Experience shows that sensitization may occur to common foods taken in excess, milk, egg and wheat being the chief offenders. Seasonal foods that are eaten at infrequent intervals and in great quantities, e.g., shell food, berries, nuts and other seasonal fruits and vegetables, are also potential sensitizers.

The practice of overfeeding infants and the present vogue for introducing many new foods very early in infancy fall into this category.

Fad diets are usually composed of a limited number of foods, and very often raw foods. It is reasonable to assume that they may lead to food sensitization.<sup>7</sup> The danger of introducing an unusual substance is exemplified in the somewhat bizarre and extreme case reported by Stuart and Farnham,<sup>11</sup> of an individual whose sensitivity to fish dated from the drinking of a can of glue on a bet.

The prophylactic measures in all these instances are obvious.

#### INHALANT SENSITIVITY

Dust sensitivity is due chiefly to exposure to specific dust allergens. Early infancy and prolonged confinement to the sickroom are particularly vulnerable periods.

In developing a prophylactic program, attention is first focused on the nursery. It should be furnished very simply, with no hangings and no heavy rugs. Everything in it should be washable. Feather pillows, comfortables, overstuffed furniture, which produce much dust, should be eliminated altogether or at least reduced to a minimum. A mattress and pillow stuffed with a good quality of hair is preferable, although good cotton linter and feather stuffed ones that are securely covered with an impervious textile may be safe. Many substitute stuffings, such as fibreglas, rubber foam, et cetera, are being developed and may prove effective.

Heavy silk and woolen materials that shed easily must be avoided, not only in the immediate environment, but also as clothes.

Furniture that gives off dust, even in other rooms, should be carefully covered with down-proof material.

Infants and young children should not be permitted to sleep with pets or stuffed toys.

It may be instructive to cite examples of contact with dust allergens. There is the striking instance of the child who from early infancy slept on a mattress containing cattle hair, and in early childhood had a hobbyhorse covered with cattle hair. Elimination of the hobbyhorse and mattress relieved his asthma.

Another child developed his first attack of asthma after lobar pneumonia at the age of two years. I discovered that he had been sensitized to the rabbit hair in pillows in the home of his grandmother, with whom he lived for a period, and to which he returned to convalesce after the pneumonia. The father was employed in a felt hat factory and subsequent attacks were traced to the rabbit fur dust adhering to the father's clothes.

An infant, whose bedroom window faced directly on a stable, became so profoundly sensitized to horse dander, and as a consequence to the related protein in horse serum, that anaphylactic shock resulted from a first small injection of horse serum.

Recently, I met a young man whose case might also be cited as a controlled experiment. He was the son of the proprietor of an inn situated directly on the shore. At the age of twelve, he became the proud possessor of a pony. The father presented each of his three sons with one on the promise that they would take care of the animals. For three months this boy currycombed and groomed his pet. Then he went off to school, while his brothers stayed at home. When he returned, after a period of eight months, he discovered that every time he went to the stable, he had a most uncomfortable choking sensation. One day a guest saw him in one of his "spells," which he recognized as asthma. Upon investigation, he proved to be skin sensitive to horse dander, and he has been clear of difficulties since he has avoided contact with horses. There was no history of allergy on either side of the family, and it is interesting that the two brothers who remained at home continuously did not develop any difficulties.

*Pollinosis* may result from undue exposure to pollens. Piness and Miller<sup>4</sup> described the interesting case of a group of city dwellers who were transferred to a mountain community, where they were exposed to unusual amount of pollens, some of which were foreign to their previous environment. As time went on, a large number developed hay fever. Family history seemed to play a minor role. Other cases, less striking perhaps, have been cited in the literature, showing the relationship of undue exposure to pollens and the consequent development of hay fever.

Such cases are very like our animal inhalation experiments.<sup>6</sup> Animals, exposed to a dust-laden atmosphere for a short period, are difficult to sensitize. As the length of the exposure is increased, a greater number of animals are sensitized. An instructive experiment was one in which

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we studied a female guinea pig and her four offspring. Three of the latter were exposed to an antigenic dust. After an interval of several weeks, the mother and the entire litter were placed in the dust chamber. The three which had been previously exposed showed signs of experimental asthma, whereas the two that had no previous contact remained unaffected.

From the standpoint of prophylaxis, the seashore or other sections of the country that are relatively free from pollen may be more advisable for vacation purposes for the infant and young child.

Insecticides which contain pyrethrum should be avoided since this ingredient appears to be a potent allergen, closely related biologically to ragweed pollen.

## DRUG ALLERGY

Although hypersensitiveness is primarily due to protein substances, it has been shown that substances other than protein can induce specific hypersensitivity. Drugs in themselves are not antigenic, but may form antigenic conjugates in combination with proteins of the animal body, called *haptens* by Landsteiner,<sup>3</sup> which are capable of inducing sensitization.

Striking instances of drug sensitivity have been reported, especially when used in large doses and in recurrent conditions. The phenolphthalein group of cathartics are notorious for their production of fixed drug eruptions. The pyramidon and allonal group have been assumed to be causative agents in the development of agranulocytosis. The indiscriminate use of external medicaments for the skin and mucous membranes has resulted in specific sensitivity.

Today, the sulfa combinations and antibiotics such as penicillin, streptomycin, have sprung into prominence and are being used to an alarming degree. Many reports have already appeared in the literature indicating that allergy may result from their repeated use. In my book<sup>9</sup> I made a plea that their indiscriminate use should be curtailed. Sensitivities arising from their use may account for much of the allergy of the future.

Infants who react severely to a drug given for the first time may possibly have been sensitized *in utero*. Caution should therefore be observed in the administration of drugs to pregnant women and nursing mothers.

## BACTERIAL ALLERGY

Our knowledge of bacterial allergy is comparatively scant, and it is therefore difficult to say how it may be successfully diagnosed and differentiated from the disease with which it is associated.

According to Zinsser,<sup>12</sup> it seems reasonably clear that in bacterial allergy we are dealing with the sensitization of the body by autolytically liberated antigenic substances which are absorbed from any focus in which bacteria react with inflammatory tissues, and as a result of which the body

is subsequently rendered sensitive to contact with these same autolytic products, whether they are liberated and absorbed from a chronically existent focus or from an identical infection subsequently acquired.

It is true that the allergic phenomenon results from a mild, non-progressive, and transitory irritation of sensitized tissue. It can, however, hardly be questioned that a body which is allergic to a given bacterial antigen is vulnerable to a degree that may lead to serious pathologic change, such as inflammation, extensive edema, hemorrhagic transudation, and even necrosis. The reactions are, as a rule, explosive in nature.

The repeated common cold or coryza may yet be proved to be attributable to an allergic basis. Zinsser described the simple experiment of taking a hot bath and then exposing oneself to cold air until an uncomfortable chilly feeling is experienced. Such a procedure usually results within twelve hours in the early signs of a cold which runs its ordinary course. According to Zinsser, this definite train of events excludes infection from without and can be explained only by one of two alternatives—either a direct invasion by bacteria previously present on a mucous membrane in which the capillary disturbances due to the chilling have permitted penetration; or, by an allergic reaction of a sensitive mucous membrane to the bacterial antigens present in the nose when the communication between tissues and surface is established by the capillary permeability resulting from the chilling. It is more than likely that human beings are all sensitive to one or more of the organisms present in their respiratory tracts and that the degree of this sensitiveness fluctuates according to the recently existing local flora. The noticeable similarity of the early stages of such reactions to the allergic conditions mentioned above, the speed of onset, and the almost bacteria-free condition of the early exudate in many cases favor an allergic mechanism.

After the allergic reaction has been provoked, it is only natural that a secondary bacterial inflammatory process should supervene. It is for this reason that all infectious processes in early infancy and childhood should be meticulously treated. The prevention of recurrent episodes should materially reduce the severity of the infections. The proper hygienic and dietary measures and the judicious use of vaccines are all efficacious in the prevention of bacterial allergy.

That so destructive a disease as rheumatism may have for its underlying mechanism an allergic reaction to some form of hemolyzing streptococcus is indicated by a great deal of experimental evidence. It is needless to say that the most important work to be done in rheumatism is preventive.

Scarlet fever, tuberculosis, and pneumonia need only be mentioned here, for there is much which is yet to be accomplished in the allergic aspects of these diseases.

It has been pointed out that certain diseases, such as pertussis, pneu-

monia, measles and scarlet fever, often antedate asthma. Whether any direct relationship exists between these diseases and the subsequent allergy is difficult to determine. An increase in membrane permeability, permitting a more ready entrance of sensitizing substances, may be an underlying factor.

Whatever the basis, it would seem reasonable to suggest that all available immunizing measures against infectious diseases should be more generally employed in childhood.

#### SERUM HYPERSENSITIVITY

Serum hypersensitivity may result from several causes. We have shown experimentally that an animal sensitized through the inhalation of horse dander may succumb to a primary injection of horse serum. Similarly, a child with horse dander or rabbit hair sensitivity may die in anaphylaxis or have a profound anaphylactic reaction when given a first injection of antiserum.<sup>10</sup>

Sensitivity to serum may result from horse or rabbit meat ingestion. This is less common in America than it is in Europe.

Sensitization to serum may result from repeated injections of antisera.

In order to prevent serum accidents, it is essential for the physician to test every child for serum sensitivity before administering an antiserum. If the child gives a systemic reaction, manifested by urticaria, or dyspnea, he should, as a rule, not be given the serum. If it is mandatory, it should be given slowly in small doses, subcutaneously, or by slow intravenous injection, diluted with saline, concomitantly with adrenaline and atropine.

Too often, tetanus antitoxin is given without adequate provocation.

It is better to treat a superficial wound surgically than to resort immediately to tetanus antitoxin. No fixed rules can be laid down, and one must be guided by the circumstances in the individual case.

In the prophylaxis of diphtheria and tetanus, toxoid is almost universally used today, which has materially reduced the incidence of serum sensitivity. It is essential that every allergic child be properly immunized, with booster doses given at subsequent intervals. The actual prevention of serum sensitivity can best be accomplished by diminishing excessive contact with horses and rabbits, by desensitization of patients sensitive to animal dander, and by a reduction in the indiscriminate use of antisera in childhood meningitis, suspected diphtheria and tetanus.

#### SUMMARY AND CONCLUSIONS

1. Allergy may develop in children whether born into allergic or non-allergic families, because all individuals are potentially capable of developing sensitivities.

2. Antigens or antibodies may be transmitted to the fetus through the placenta. Unaltered proteins may pass through the walls of the digestive

tract or the upper respiratory tract. Unaltered allergens may enter the blood stream by way of the skin or by parenteral injection.

3. The acquisition of hypersensitiveness depends upon: (a) constitutional or other factors peculiar to the individual, (b) the nature of the exciting substances, (c) the amount of antigen to which the individual is exposed, (d) the amount of native antigen which actually invades the blood stream, and (e) the intervals at which such exposures occur. In my estimation quantitative factors play a larger role than do qualitative ones.

4. Intra-uterine life, infancy, illness and convalescence constitute vulnerable periods, during which the individual must be protected especially from undue exposure to highly antigenic substances.

5. Much can be accomplished prophylactically in the management of the pre-allergic child by the adoption of measures which aim to prevent the inception of food, dust, drug, serum and bacterial sensitivity through the regulation of the diet, the management of the environment, the control of drug and serum therapy, and the reduction of recurrent invasions of pathogenic agents.

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## THE TOPICAL APPLICATION OF THEPHORIN IN PRURITIC DERMATOSES

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THE specific treatment of allergic dermatoses is, unfortunately, disappointing, and there have been but few notable advances in recent years. Specific hyposensitizing measures have not proved of much value in contact dermatitis due to poison ivy or other plants, atopic dermatitis, urticaria and dermatoses produced by drugs and physical agents. It is not surprising, therefore, that efforts have been made to treat various allergic dermatoses by nonspecific means. Unfortunately, in most cases the older non-specific remedies such as histamine, histamine protein conjugate (Hapamine), and histaminase all proved about as disappointing as the specific measures.

In 1936 Dragstedt and Mead<sup>2</sup> reported experiments indicating that many of the major symptoms of anaphylactic shock could be accounted for by the quantity of active histamine present in the blood and lymph at the time the reaction occurred. These and other experiments have stimulated various workers to develop drugs which are capable of diminishing or preventing several of the pharmacologic effects of histamine.

Fourneau<sup>4</sup> and his French associates developed the first of the so-called antihistaminics or histamine antagonists and since then, as is well known, numerous compounds have been evolved many of which have a clinical effectiveness without prohibitive side effects. These agents, when administered orally, are undoubtedly of value in certain allergic dermatoses such as urticaria (both acute and chronic), urticarial drug eruptions, some physical allergies, some cases of pruritus ani and vulvae, and in a few cases of atopic and contact dermatitis. The fact that the oral administration of the histamine antagonists is of value in the treatment of allergic dermatoses led to the hope that the topical application of these drugs might be of additional help.

In 1947, Mayer<sup>5</sup> reported experimental epidermal sensitization to paraphenylenediamine in guinea pigs. He showed that greater protection to subsequent applications of the chemical could be obtained by the local application of 5 per cent triplennamine hydrochloride (Pyribenzamine) in sesame oil than by the parenteral injection of the same drug. He theorized that this was brought about because there was a higher concentration of the drug at the test site plus the influence of a possible effect of local anesthesia.

In 1947, Feinberg and Bernstein<sup>3</sup> used 2 per cent Pyribenzamine ointment in thirty-three cases of atopic dermatitis of varied extent, chronicity and severity. All of the patients were studied for allergic factors and

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the majority disclosed definite cutaneous reactions and observations which indicated a relationship between the eczema and specific allergenic causes. They reported that twenty-four of the patients noted consistent relief from the use of the ointment. In most instances the greatest relief was obtained in patients whose lesions were localized to small areas. A combination of oral and topical medication seemed most beneficial although in a few instances the local or oral treatment was the only one effective. In a few patients the ointment was irritating, especially those in which the lesions were acutely inflamed. The Pyribenzamine ointment gave symptomatic relief to eight of nine patients with pruritus ani. In two patients with contact dermatitis of the eyelids, two of dermatitis of the arms of unknown nature, and one of dermatitis of the legs of unknown cause, improvement in the itching was obtained. In a patient with urticaria, the pruritus caused by the individual lesion was relieved by the application of the ointment while in four other cases of dermatitis no benefit was obtained. Sulzberger, Baer, G. Rubin and others<sup>10</sup> working with Pyribenzamine cream at the New York Skin and Cancer Unit obtained results which were somewhat in contrast with those of Feinberg and Bernstein. Sulzberger and his colleagues found that the only dermatitis in which local application of Pyribenzamine cream was of antipruritic value in a significant proportion of cases was lichen chronicus circumscriptus (circumscribed neurodermatitis). Local application of the antihistaminic agent was not only of no value but even aggravated the lesions of atopic dermatitis (disseminated neurodermatitis) in most of their cases.

Friedlaender and Feinberg<sup>5</sup> showed in 1946 that the local application of a solution of beta-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) to a scratch on the skin of an allergic person inhibited the normal whealing from histamine or that from an antigen such as ragweed. These workers also showed that solutions of histamine antagonists could penetrate the unbroken skin. This was demonstrated by applying the antihistaminic to an area of dermatographic skin and then stroking the part and the contiguous untreated skin. Whealing took place only at the untreated areas, skipping the treated site.

Leavitt and Code<sup>6</sup> experimentally demonstrated the anesthetic action of Benadryl in the skin of human beings. The drug was injected intracutaneously on the flexor surface of the forearm and was found to produce more intense anesthesia than injections of procaine of comparable strength. There was no apparent correlation between the anesthetic effect and the antihistaminic activity.

In 1947, Perry<sup>9</sup> reported on the local use of Benadryl ointment. Two per cent Benadryl was incorporated in a water-soluble ointment base and applied to the skin. The effect on the wheals and erythema produced by intradermal injections of 0.1 c.c. of 1:100,000 dilution of freshly prepared histamine phosphate was studied. He found that there was no significant

difference in the diameter of intensity of the erythema and the wheal produced by histamine, with or without the ointment. The same preparation was applied topically in twenty-two patients with various pruritic dermatoses. There was no supplemental therapy. Six patients had moderate and two had excellent relief of the pruritus. Four of these, however, had the same degree of relief from the ointment base alone. Perry believed that his studies indicated that Benadryl in the preparations studied was probably not absorbed in sufficient quantities to produce a clinical effect following local application and that it had no significant antipruritic effect.

Thenylpyramine hydrochloride is also available for topical application (cream Histadyl Hydrochloride, Lilly). The drug is incorporated in a greaseless ointment base in a concentration of 2 per cent and is claimed to be of value in allergic contact dermatoses and for local analgesic action in pruritus ani and vulvae. Although no references were quoted, the firm which markets the product stated in its literature that clinical reports were obtained from twenty-three different observers: "Of seventy-three cases of allergic contact dermatitis which were not eczematous, sixty-two responded favorably. Six of eight cases of dermatitis due to poison ivy were relieved following local application of the cream. Of forty-five cases of allergic eczema, twenty-seven were reported as showing satisfactory response. Of seven cases of pruritus ani or pruritus vulvae, six had some degree of relief and one was not benefited. As a rule, urticaria and neurodermatitis were not improved to any significant degree. In some instances contact dermatitis responded better to both oral and local administrations of the drug than to local treatment alone. Sixteen cases of acute allergic dermatitis due to contact with various drugs cleared promptly upon application of the cream, but the dermatitis returned when contact with the allergenic drug was returned. One patient with eczema of the face of years' standing was relieved of itching within an hour, and the eruption had completely disappeared after three weeks' treatment. The allergen was thought to be egg, and contact with egg was being avoided. The eruption reappeared four months later and was again relieved by prompt resumption of treatment. One case of contact dermatitis was due to a rare chemical with which the patient was of necessity in contact at intervals of a few months. Relief was obtained by both oral and local administration. When contact with this chemical was again necessary, oral and local therapy was begun at the first appearance of dermatitis, with resultant relief." It is difficult for us to interpret these results.

Thephorin, the drug used in this investigation, differs chemically from the ethylenediamine derivatives (Antergan, Neo-antergan, and Prybenzamine) and the closely related diphenylhydramine compounds (Benadryl and Hydryllin). Thephorin base is a brand of phenindamine which is a polycyclicamine. The oral forms of the drug, syrup and tablet, contain

the hydrogen tartrate salt of the Thephorin base which is also used in the ointment. The formula for the Thephorin base is 2-methyl-9 phenyltetrahydro-1-pyridindenc.

In August 1948, Wooldridge and Joseph<sup>11</sup> reported the results of the use of Thephorin in the treatment of disseminated neurodermatitis. Their patients were treated with the syrup and tablets orally in addition to the topical use of 5 per cent Thephorin in a carbowax vehicle. Twenty-one patients were treated with both local and oral medications and two patients received only the ointment. The degree of involvement varied from that of a mild cubital or periorbital eruption to acutely pruritic and exudative eruptions involving most of the flexural areas. The duration of the disease varied from two weeks to seventeen years and the period of treatment from one to seven weeks. Treatment was carried out during the severest part of the winter and the results did not include any period during which spontaneous seasonal clearing, which is so often observed, could be noted among other such patients. The results of treatment were as follows:

Complete clearing .....	2
More than 75 per cent but less than complete clearing.....	7
More than 50 per cent but less than 75 per cent clearing.....	8
Benefited but less than 50 per cent clearing.....	2
Not benefited .....	3
Became worse (although patch tests were negative).....	1

For a period of two weeks, three patients received Thephorin orally together with tars and other medications before Thephorin ointment arrived. No benefit attributable to oral Thephorin could be noted. A control series of six patients was also treated. One cleared completely with application of a carbowax base only, while the remaining five showed conclusive improvement in the areas treated with the Thephorin ointment but no improvement in those treated with the ointment base alone. In four of the twenty-three patients the oral medication was discontinued because of side effects of irritability and sleeplessness. In these patients the lack of oral medication did not seem to slow the rate of improvement. The authors believed that it was likely, in view of the consistent failure of previous antihistaminic drugs in the treatment of disseminated neurodermatitis, that Thephorin has a mode of action which is distinctly different from the others since it is not a significantly more powerful antihistaminic agent.

#### PERSONAL EXPERIENCE WITH THE TOPICAL APPLICATION OF THEPHORIN

The purpose of this study was to investigate changes in the subjective and objective signs in common dermatoses which could be obtained by the application of 5 per cent Thephorin incorporated in carbowax 1500.\* Most of the patients were advised to apply the ointment thinly as frequently as was necessary to allay itching. Unmedicated carbowax 1500

\*Supplied by Hoffmann La Roche, Inc., Nutley, New Jersey.

was substituted for the Thephorin at times in an attempt to evaluate the psychologic effect of the therapy and the effect of the vehicle itself as a lubricant.

Sixty per cent of the fifty-eight cases which were treated with Thephorin ointment were circumscribed neurodermatitis. The average age was 39.3 years and there were 57 per cent males and 43 per cent females. The average duration of the disease was about five years. Most of the patients (38.2 per cent) had received previous therapy in the form of various topical applications including roentgen radiation as well as oral antihistaminics and sedatives. Approximately half of the patients presented single lesions while the rest had multiple plaques. Twenty-five per cent presented lesions on the anogenital region, 25 per cent on the neck, 25 per cent on the legs, 10 per cent on the nuchal region, 10 per cent on the arms, 5 per cent in the ears, and 5 per cent on the lids. Only one patient in thirty-four presented lesions on the trunk. The duration of treatment with 5 per cent Thephorin ointment varied from three days to three months. Forty-four per cent were treated one week or less; an additional 21.5 per cent from one to two weeks, and 34.5 per cent for periods varying from two to twelve weeks. The results following the application of Thephorin ointment were as follows:

	<i>Objective</i>	<i>Subjective</i>
Excellent .....	6 (17.6%)	6 (17.6%)
Moderate improvement .....	19 (55.9%)	22 (64.7%)
No change .....	5 (14.7%)	2 ( 5.9%)
Worse .....	4 (11.8%)	4 (11.8%)

Three patients reported relief of varying degree when the preparation was first used but within a short time the efficacy diminished so that some other preparation had to be used. One patient stated that the unmedicated carbowax 1500 base was equally effective as the Thephorin ointment and another believed that Pyribenzamine cream was equally effective as the Thephorin ointment. In one patient whose eruption flared following the use of the Thephorin ointment a patch test was negative at 48 hours. Two other patients developed folliculitis following the use of the preparation.

There were nine patients with disseminated neurodermatitis (atopic dermatitis). The average age was 24.5 years. Of this group 77 per cent were male and 23 per cent female. In 50 per cent of the cases the eruption had been present since infancy or childhood while in the others the duration of the eruption averaged over four years. All of the patients had been previously treated by various methods. Fifty-five per cent of the patients presented exudative lesions. The results were as follows:

	<i>Objective</i>	<i>Subjective</i>
Excellent .....	0	11.1%
Moderate improvement .....	55.5%	22.2%
No change .....	0	33.3%
Worse .....	44.5%	33.4%

One patient obtained symptomatic relief for one month, following which she flared and presented a positive patch test to the preparation.

The next group was made up of seven patients who presented eczematous eruptions which we were unable to classify. The results were as follows:

	<i>Objective</i>	<i>Subjective</i>
Excellent .....	43%	14%
Moderate Improvement .....	57%	86%
No change .....	0	0
Worse .....	0	0

The Thephorin ointment was also used topically in two cases of lichen planus, both of whom obtained definite relief from pruritus. In one the relief was striking. In one case of psoriasis involving the scalp, thighs, ankles, and perianal region there was relief from itching. One patient who had stasis dermatitis stated that a tar paste was equally effective as Thephorin ointment. One case of dermatophytosis of the feet and ankles was aggravated by the preparation and obtained no relief from itching. Another patient who had erythematous squamous seborrheic dermatitis of the ear canals obtained temporary objective and subjective improvement but flared six weeks after she had been using the ointment. A positive patch test was obtained. In a case of generalized idiopathic pruritus without cutaneous eruption there was no relief following the application of Thephorin ointment. Since the number of cases of each dermatosis in this miscellaneous group is so small it is impossible to draw conclusions regarding the value of Thephorin ointment.

In eighteen cases, 5 per cent Thephorin lotion was used rather than the ointment. The lotion was selected because the eruptions were acute, extensive, and exudative. Eleven of the patients were diagnosed contact dermatitis and seven, neurodermatitis. Five of the eleven patients had acute contact dermatitis due to poison ivy and all experienced prompt relief of pruritus. Two-thirds of the remaining six who had contact dermatitis experienced relief of itching. Three of the seven cases of neurodermatitis presented dry lichenified plaques while four showed more acute, eczematous lesions. Two of the three patients with dry lesions experienced relief of pruritus and to our surprise, all of the four patients with eczematized lesions were relieved. There were no exacerbations which were attributed to the application of the lotion.

#### COMMENT

Most of our cases were circumscribed neurodermatitis. We were especially interested in the antipruritic value of Thephorin ointment in this type of dermatitis. About 80 per cent of the patients obtained gratifying relief from pruritus. Many of these individuals stated that Thephorin ointment was far superior to any other topical application which they had used. Because of the fact that other agents, especially roentgen

radiation, were used we do not feel qualified to analyze the objective results. We believe that it is permissible to say that Thephorin ointment is an efficient antipruritic and only occasionally produces irritation. It is our distinct impression that the application is more effective in dry lesions and is more apt to aggravate exudative lesions. The ointment was especially effective in anogenital pruritus with lichenification (included in our group of circumscribed neurodermatitis). The objective and subjective improvement was excellent in thirteen out of the fourteen cases of this type.

Because of the relatively small number of cases of atopic dermatitis, far-reaching deductions cannot be drawn. We feel, however, that the preparation is relatively ineffective in this dermatosis since none of the cases obtained startling objective improvement and only 10 per cent excellent subjective improvement. There were a few other cases in which some improvement occurred but it is impossible to determine whether the improvement was the result of the application of the Thephorin ointment. In contrast, one-third of the patients complained that their symptoms were more intense and almost one half were objectively worse.

In the few cases of acute dermatitis in which Thephorin lotion was used it proved to be an effective antipruritic agent. We gained the impression that the lotion was more satisfactory than the ointment in exudative lesions.

From our studies we have been unable to elucidate the mode of action of Thephorin as used topically as an antipruritic. According to Bishop<sup>1</sup> itching is a modality of pain and is most easily elicited at central pain spots. He believes that itching represents a summation of weak sub-threshold pain stimuli. Lehmann<sup>7</sup> has shown that Thephorin possesses a potent local anesthetic action. On the rabbit's cornea 1 per cent solution of Thephorin produced deep anesthesia lasting twenty-nine minutes. Using the intracutaneous wheal test on guinea pigs, Thephorin produced local anesthesia of longer duration than procaine hydrochloride. This may be the explanation of its antipruritic action in the human skin. The other possibility is that enough of the preparation penetrates the integument to produce an appreciable local antihistaminic effect.

#### CONCLUSIONS

1. On the basis of our experience, Thephorin used topically is an effective antipruritic agent in circumscribed neurodermatitis.
2. *It is especially effective in anogenital pruritus with lichenification.*
3. It is more effective on dry lesions and more likely to produce irritation on exudative lesions.
4. The topical use of Thephorin ointment in disseminated neurodermatitis (atopic dermatitis) was not particularly encouraging.
5. The number of cases of miscellaneous dermatoses was too small to draw any definite conclusions.

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# POLLEN SURVEY OF LOS ANGELES 1941-1945

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Los Angeles, California

THE HAY-FEVER flora of the Los Angeles area has been adequately described<sup>6,15,17</sup> but information relative to the local pollen counts and seasons remains meager. Reports presently available<sup>3,4,7,18</sup> fail to encompass a year's period, or list total rather than differential counts, or exhibit both defects.



This paper presents the differential counts accumulated at a single station in Los Angeles over a period of five years.

## METHOD

Since wartime exigencies made it impossible to use the roof of a tall building for the duration of this study, the place of exposure was a residence in the Silver Lake neighborhood. The exposure technique consisted

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## TABLE I. TREE POLLEN COUNTS

		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Yearly Totals	Highest Count And Date
Acacia	1941			3	4	2	3		1	1	1			15	
	1942		3	2	1	1	5	4						16	
	1943	1	2				2			2				7	
	1944		4	5	1		4		1					15	
	1945	4		1	1	1		1	1					9	
	Aver.													12	
Alnus (Alder)	1943	19	3											22	
	1944	26	1									2		29	
	1945	36	4											40	
	Aver.	27	3											30	
Cupressaceae (Cypress family)	1942	35	50	104	63	6							22	280	18, Apr. 3
	1943	10	52	49	36	3								150	8, Feb. 1
	1944	10	37	66	17	5							3	138	6, Mar. 11
	1945	9	44	15	16	4							12	100	8, Feb. 7
	Aver.	16	46	59	33	5							9	167	
Eucalyptus	1941		4	0	3	4	2	1	2	1		2	6	25	
	1942		1	3	1		1	1	1				1	9	
	1943	3	1	1	2	1				2			1	11	
	1944	1	1	1	1		1			2	1			8	
	1945	1	1	1	1	1		3	3			1		12	
	Aver.													13	
Juglans (Walnut)	1941			8	84	48	1							141	10, Apr. 8
	1942			39	91	67	3							200	18, Apr. 23
	1943			21	71	35	1							128	7, Apr. 1
	1944			39	143	52	4							238	19, Apr. 16
	1945		2	20	64	40	2							128	6, Apr. 28
	Aver.			25	91	48	2							167	
Olea (Olive)	1941				11	55								66	5, May 7
	1942				9	32	2							43	3, May 5
	1943				13	29								42	2, various times
	1944				7	37	1							45	4, May 3
	1945				8	33	3							44	2, various times
	Aver.				10	37	1							48	
Pinaceae (Pine family)	1941		4	52	15	5	2	1	2	5	1	1		88	8, Mar. 1
	1942	1	40	31	20	14	56	10	2	8	55	6	1	244	9, June 15
	1943		45	11	12	7	14	1	1	4	2			97	4, Feb. 14
	1944		21	59	13	8	16	7	5	4	69	14	1	217	5, Mar. 8
	1945	4	42	24	21	12	5	4	1	3	11	9	1	137	5, Feb. 17
	Aver.		30	35	16	9	19	5	2	5	28	5		157	
Platanus (Sycamore)	1942			10										10	
	1943			26	2									28	
	1944			14										14	
	1945		3	13	5									21	
	Aver.			16										18	
Quercus (Oak)	1941			30	81	48								179	16, Mar. 17
	1942		11	284	125	98								518	73, Mar. 27
	1943			30	49	7								86	9, Apr. 1
	1944		7	154	146	30								339	32, Mar. 30
	1945			10	86	10								106	6, Apr. 6
	Aver.			105	97	39								246	
Salix (Willow)	1943			6										6	
	1944			2	11									13	
	1945			2										2	
Ulmus (Elm)	1942							2	80	3	1			86	13, Sep. 10
	1943							4	10	6	3			23	2, Sep. 14
	1944								9	6				15	2, Sep. 25
	1945								3	37				40	15, Oct. 1
	Aver.								2	25	13	1		41	

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TABLE II. GRASS POLLEN COUNTS

		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Yearly Totals	Highest Count and Date
Gramineae	1911			22	80	130	81	95	55	53	71	29	10	626	11, May 26
	1912	2	5	28	41	142	158	205	92	93	78	18	5	870	12, July 7
	1913	1	2	20	59	147	81	105	88	68	62	19	10	662	16, May 14
	1914	1	3	23	67	119	59	24	77	28	30	7		438	7, few times
	1915	2	3	18	45	81	63	45	48	43	20	8	2	381	6, few times
	Aver.	1	3	22	59	124	88	95	72	57	52	16	5	595	

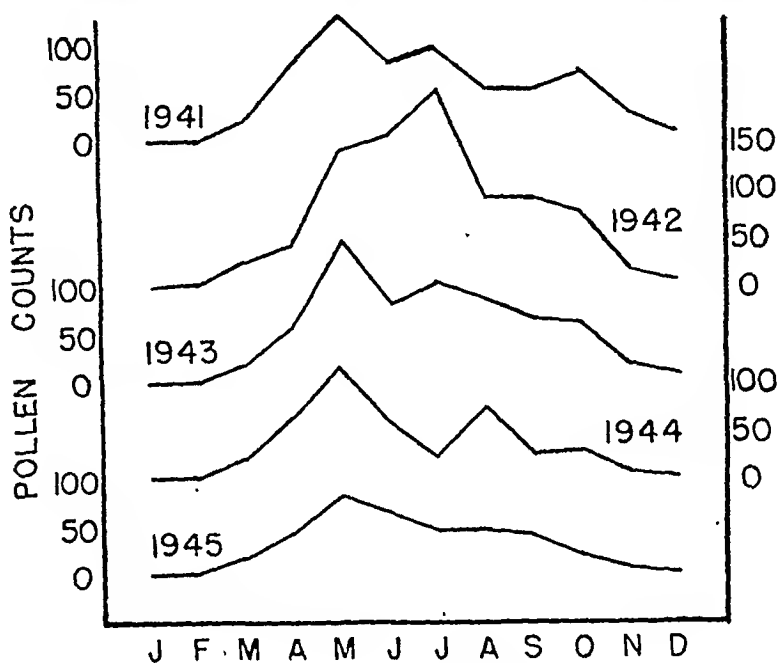


Fig. 1. Annual grass seasons.

in placing a vaseline-coated slide on a window sill of a roofed-over porch facing, and open to, the west. A slide was set out at approximately 8 a.m. every day when counts were relatively high, otherwise every two or three days. Pollen counting was done with the aid of an inclined binocular microscope with a 10X ocular and 10X (16 mm.) objective. The measured width of the field at this magnification was 1.6 mm. The standard slide being 1 x 3 inches, one sweep across the width of the slide covered an area of 40.6 ( $= 25.4 \times 1.6$ ) sq. mm., and five such sweeps an area of 203 ( $= 5 \times 40.6$ ) sq. mm., or approximately 2 sq. cm.

The counts presented in this paper are based on this area of two square centimeters.

While most of the pollen grains seen on the slides have been identified over the five-year period, a few are still of unknown origin. Some are seen unpredictably at rare intervals. Others, also minimal in number, are noted seasonally.

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### TREES

Table I presents the tree pollen counts. (In a few instances, e.g. alder, the counts for the first year or two were not carried out.)

The low numerical value of the counts in this and succeeding tables has necessitated a grouping of the data by months in order to obtain a meaningful picture of the seasonal fluctuations. This is in contrast to reports from other areas where the counts are grouped by periods of a few days.

In the case of *Acacia* and *Eucalyptus* the pollens appear in such few numbers sporadically throughout the year that no attempt has been made to determine their average monthly totals. (Pollen of the *Palmaceæ*, not listed in the table, similarly occurred in negligible quantity.)

An interesting finding with respect to elm is that the pollen was noted at this station only in the fall, not in the spring as in the East. The source of the pollen is discussed below.

### GRASS

The counts for grass are assembled in Table II. Figure 1 depicts the seasonal fluctuations. The pattern of atmospheric incidence is as follows:

At rare intervals from mid-December through February, a single pollen may be noted as a wind-blown relic of the previous season. In March, the count begins to climb progressively upward until the height of the season is reached during the latter part of May and first part of June. From then onward to mid-December, the trend is downward, but temporary recrudescences may occur during this period. In fact, the July counts of 1942 were the highest for the year.

### WEEDS

Table III summarizes the weed counts.

An unexpected finding is the definite, though minimal, increase in the ragweed count which takes place in the month of May in addition to the usual fall increase. This is clearly demonstrated in Figure 2.

Interesting also is the recurrence of artemisia pollen in January of 1942 and of 1944. Ordinarily, this pollen disappears from the air in early December. The phenomenon has been explained by the Smalls<sup>17</sup> as being due to the fact that in the foothills of the interior ranges the pollinating habit of *Artemisia californica* is different from that which the species exhibits on the coast. Inland, its pollination is dependent upon the rainfall, and when the fall precipitation is too light the plant awaits the heavier rains of late December or early January to complete its flowering.

Figure 3 shows the average seasonal fluctuations obtained at this station for the pollens of major clinical importance.

### DISCUSSION

The observations reported above are similar to those reported from other areas of the South and Southwest with regard to (1) the occurrence of two annual atmospheric waves of ragweed pollen, (2) the presence of a

# POLLEN SURVEY OF LOS ANGELES—TARGOV

## TABLE III. WEED POLLEN COUNTS

		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Yearly Totals	Highest Count and Date
Ambrosiaceae (Ragweeds)	1941				3	8	1	8	5	33	40	3	1	118	5, Oct. 1
	1942				2	14	1		11	35	20	5	2	91	5, Sep. 21
	1943				2	13	2	5	11	46	18	2	1	100	4, Sep. 23
	1944				4	12	1	1	8	20	20	1	1	70	3, Oct. 4
	1945				6	5		1	3	29	23	3	0	74	6, Oct. 1
	Aver.				3	10	1	3	8	33	24	3	1	91	
Artemisia (Sagebrush)	1941							1	8	24	20	46		100	8, Nov. 8
	1942	3						1	1	9	8	19		38	3, Nov. 14
	1943							1	1	6	5	5	2	20	1, Various times
	1944	6						1	4	9	11	2	1	28	1, Various times
	1945								1	6	17	11	2	37	2, Oct. 24
	Aver.							1	3	11	12	17	1	45	
Chenopodiaceae- Amaranthaceae	1941			1	7	9	17	7	11	6	1			59	2, Various times
	1942			2	1	1	3	1	7	2	2			19	1, Various times
	1943			1	2	1		1	6	2				13	1, Various times
	1944			4	1	2	4	1	9	5	1			27	1, Various times
	1945				2	3	10	10	10	8	2			45	2, Various times
	Aver.			2	3	3	7	4	9	5	1			33	
Fern	1942							1	8	5	7	1	1	23	
	1943	1				1		2	5	10	6	6	2	33	
	1944								3	4	3			12	
	1945	1	2					2	6	3				14	

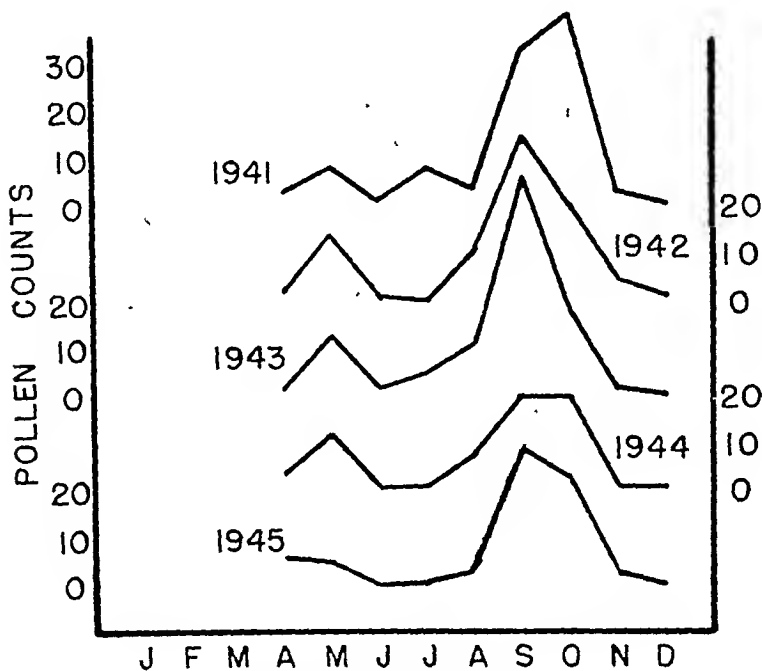


Fig. 2. Annual ragweed seasons.

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fall-pollinating elm, (3) the prevalence of generally low counts and (4) the prolonged, overlapping seasons:

1.. The phenomenon of two ragweed seasons for the year is engendered by the presence of various species of spring-flowering ragweeds coexisting

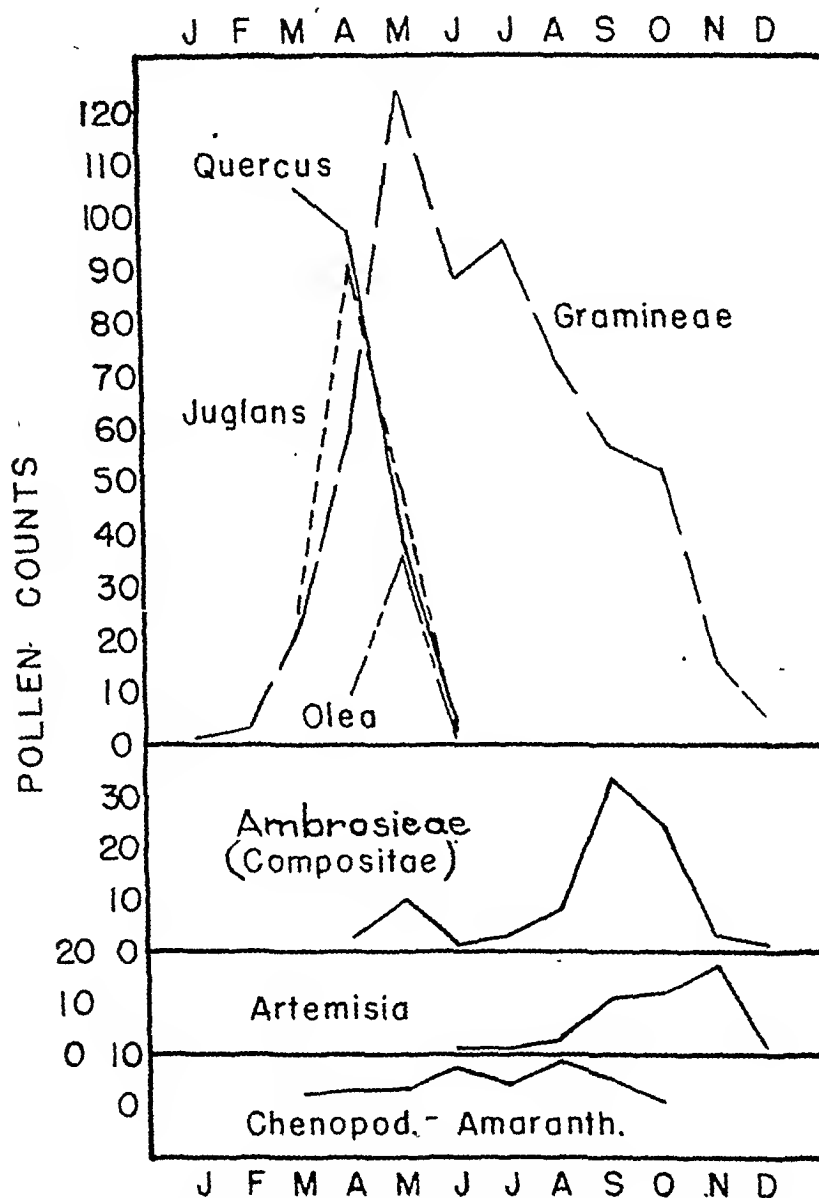


Fig. 3. Pollen seasons of Los Angeles, five-year averages, Silver Lake Station.

with the usual fall-blooming ones. Watson and Kibler<sup>21</sup> reported this spring ragweed season in the Southwest some years ago, and stated that it was due to *Franseria deltoidea*. Phillips<sup>13</sup> later studied the matter more intensively and pointed out that additional spring pollinators such as *F. dumosa* and *F. ambrosioides* are present in the Salt River Valley, in which Phoenix is located, and that in other valleys farther south and west

*Hymenoclea salsola* similarly flowers in the spring. Durham,<sup>5</sup> on the basis of Rydberg's<sup>16</sup> study of the distribution of *F. dumosa*, states that a spring ragweed season is present in the Mojave Desert also, and southward from there to Lower California. This has been verified recently by Harsh,<sup>8</sup> who, in a zone made up of contiguous portions of California, Arizona, and Mexico, finds a spring ragweed season due primarily to *F. dumosa* and possibly also to *H. salsola*.

These desert ragweeds are not found in this coastal area. Here<sup>6,15,27</sup> the earliest spring-flowering composites of importance in allergy are *F. bipinnatifida* (beach bur), *Xanthium canadense* (cocklebur), and *Xanthium spinosum* (spiny cocklebur).

The two species of *Xanthium* may be dismissed from consideration as contributing to the spring rise in atmospheric ragweed pollen. For one thing, the distinctive pale "pebbled" grains of cocklebur have up to this time not been noted at this station. But more decisive than the restricted distribution of the genus is the fact that field observations reveal that the peak of pollen production of both species is not reached till midsummer\* or after.

*F. bipinnatifida*, on the other hand, ranges all along the coast of California, and while it blooms at any time from April into fall, it may be observed that optimum opportunity for collection of its pollen generally takes place in early May.\* The conclusion is inescapable at the present time that this species must account almost entirely for the spring wave of ragweed pollination.

The situation here thus duplicates what has been reported from San Diego County by Harsh.<sup>8</sup> At Alpine, California, Harsh finds that a striking rise in ambrosia-like pollen occurs during April and May, and he concludes that this can come only from *F. bipinnatifida*. The charts in his report show that a spring ragweed season takes place in the city of San Diego too, and Stealy's<sup>19</sup> charts of the atmospheric pollen of San Diego for 1936 likewise reveal this phenomenon.

While the two ragweed seasons in the desert are separated by a time interval, during which no pollination occurs, climatic conditions here induce *F. bipinnatifida* to flower continuously or remittently into the fall so that its flowering season ultimately merges with that of the late summer and early fall-blooming species (*Frauseria acanthicarpa*, *Ambrosia psilostachya*). Except for July of 1942 and June of 1945, ragweed pollen was found on the slides each month from April through November of each year, albeit in minimal or negligible quantity during the summer months. The exaggerated spring outburst of pollination must be attributed to a characteristic pollinating habit of *F. bipinnatifida* in this latitude. Obviously, vagaries in this pattern of pollination may be expected to take place contingent upon weather conditions. Thus, in Figure 1, one sees an

\*Personal communication from Mr. M. E. Webb, Hollister-Stier Laboratories.

additional wave in July of 1941, and in April of 1945 the count was as high as for May.

The occurrence of a definite rise and fall in the amount of atmospheric ragweed pollen in the spring has not previously been reported from Los Angeles. The finding demonstrates once again the necessity of making routine pollen counts in addition to field observations in order to establish local patterns of fluctuation in air-borne pollen incidence. Such patterns cannot be deduced from field observations alone.

2. The presence of a fall pollinating elm in the Los Angeles area has likewise not been previously commented upon in the literature of allergy. Black and Durham<sup>1</sup> have reported the presence of two fall-pollinating species elsewhere in the South, *U. crassifolia* (in the central and northern portion of Texas, and adjoining portions of Oklahoma and Arkansas) and *U. serotina* (in Tennessee and adjoining states).

The species here is *Ulmus parvifolia*. This species has the striking characteristic of not being deciduous in this climate, although in very cold weather it may tend to drop some leaves. For this reason, it is sometimes termed the evergreen elm, or evergreen Chinese elm to differentiate it from *U. pumila* (Siberian or dwarf Asiatic elm) which in lay parlance is also sometimes called Chinese (or dwarf Chinese) elm. Horticulturists here distinguish also a variety of *U. parvifolia* which is called *U. semper-virens*, a tree which is purported to have a more droopy habit and smaller leaves than *U. parvifolia*. The fact that it is not deciduous has made the evergreen elm by far the most popular and predominant one here in recent years, so that it greatly outnumbers other species encountered to date. These, in order of frequency, are *U. pumila*, *U. americana*, and *U. campestris* (English elm). The last named is quite rare. The American elm is noted only occasionally except in Beverly Hills. This municipality occupies an area of about five square miles within the confines of Los Angeles, its central portion being located approximately eight miles from this station. Within this territory, the Beverly Hills Park Department has planted almost 4,000 specimens of *U. americana*. Despite this massed stand, it is of interest that no elm pollen has been noted on the slides in the spring.

Predominance of *U. parvifolia* is not confined to Los Angeles, but is reported from other Southern California communities as well.\*

In view of the reputed<sup>1</sup> allergenic potency of its pollen, it is apparent that the elm must be kept in mind as a potential factor in clinical allergy in both spring and fall in this area.

3. The lack, up to the present time, of standardized techniques of exposure and counting makes it difficult to compare with any exactness the

\*In Pasadena,<sup>2</sup> only one other species is stated to be present: *U. pumila*. In Santa Barbara,<sup>20</sup> two others are listed: *U. americana* and *U. campestris*. In Santa Monica,<sup>30</sup> Hastings describes five others: *U. americana*, *U. campestris*, *U. foliacear*, *U. hollandica*, and *U. pumila*, so that this community contains six of the nine species which McAlinn and Maino<sup>11</sup> state are present on the Pacific Coast, the three others being *U. alata*, *U. fulva*, and *U. glabra*.

counts obtained here with those reported from other parts of the country. It is obvious however that for most part the counts here are minimal. To midwest allergists this is particularly noticeable in the case of ragweed. Such low counts tend to be misleading with respect to the incidence of clinical allergy here, so that it is not amiss to emphasize again, as was done previously by Piness<sup>14</sup> and by Stealy,<sup>10</sup> that there is no dearth of clinical pollinosis in Southern California. It is evident that our minimal counts are adequate to induce sensitization, although they may ensure that the severity of the resulting symptoms is less, generally speaking, than is the case in high count areas.

4. The tables reveal that as early as April one may encounter in the air such diverse pollens as those of the amaranth-chenopod group, the grasses, and ragweed in addition to the usual tree pollens such as oak, walnut, and olive. As late as October, one may still find represented the amaranth-chenopod group and the grasses, in addition to the usual fall types, such as artemisia and ragweed. These prolonged seasons are of course a function of the climate and have been reported from other favorable climates, as for example those of New Orleans<sup>12</sup> and Florida.<sup>22</sup> Wodehouse,<sup>22</sup> in this connection, has vividly portrayed the effect of southern latitudes in altering permanently the pollinating habit of ragweed from that shown by the plant in the north.

The data of this survey may be considered as being reasonably accurate for the Los Angeles coastal plain, but a problem that invites consideration is that of the possible variations to be met with in the surrounding territory. The topography of Southern California is featured by a remarkable diversity over relatively short distances. The resulting differences in conditions of temperature, humidity, precipitation, and altitude may produce a noticeable alteration, as the Smalls<sup>17</sup> have pointed out, in the flowering times of certain species within the short span of miles between the coast and both the foothills and heights of the interior mountain ranges. The degree, therefore, to which the present findings reflect the situation in areas adjacent to the coastal plain can be determined only by carrying out the manifest need for pollen surveys from several different stations.

As for the possible clinical importance of the unidentified pollens observed on the slides, one may state without hesitation that their role, if any, in the production of allergy must be minor. This is so not only because of their infrequent appearance and few numbers, but, what is more important, no distinct group of cases has as yet been delineated which parallels the time of appearance of these unknowns.

#### SUMMARY

A five-year study of the atmospheric pollen concentrations and pollen seasons at a single station in Los Angeles reveals that the pollen counts are low, and the seasons more prolonged and overlapping than in the Midwest and East.



## POLLEN SURVEY OF LOS ANGELES—TARGOW

The pollens of the trees are dispersed throughout the year as follows: Acacia and Eucalyptus, on intermittent occasions at any time of the year. Cypress family, beginning somewhat before the first of the calendar year and continuing through April. Alder, chiefly during January. Pine family, February through November. Sycamore, March and part of April. Oak and walnut, from approximately the first of March through May. Willow, on occasion during April. Olive, middle of April to the first part of June. Elm, latter part of August into October.

Pollen of grass is noted very rarely in the period from mid-December to March. The count then increases rapidly to a peak during the latter part of May and first part of June, then declines gradually, with some recrudescences, over the remaining months to mid-December.

Pollen of the chenopod-amaranth group is found from March through October with somewhat increased incidence from June through September. Ragweed pollen occurs from April through November and gives rise to two seasonal waves: a minimal one in May, generally, and a maximal one from the latter part of August through October.

Sagebrush pollen is present from July into December, with a definite seasonal upswing during September, October, and November. In some years, a brief recurrence in January takes place.

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I am indebted to the following for help in preparing this paper: Prof. O. A. Plunkett, Department of Botany, University of California, Los Angeles; Prof. W. C. Putnam, Department of Geology; Mr. J. Dorfman; Mr. Samuel Miller, Senior Observer of the U. S. Weather Bureau, Los Angeles; and Mr. M. E. Webb of the Hollister-Stier Laboratories.

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(Continued on Page 722)

# THE HEART IN BRONCHIAL ASTHMA

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THE difficulty in diagnosing bronchial asthma, especially in advanced age, lies in differentiating cardiac and pulmonary asthmatic involvement. We have various laboratory and diagnostic tests—blood eosinophilia, intradermal, patch-tests—which are supported by experienced history-taking to avoid serious mistakes that may influence the success or failure of the proposed treatment of the case in hand. Nevertheless, there are certain border states where cardiac and asthmatic conditions appear side by side. The purpose of this report is to point out how far cardiac and circulatory changes follow the asthmatic state without actual primary myocardial damage.

The first question in considering the heart and circulation in bronchial asthma is whether the physical and electrocardiographic changes are due to anaphylaxis and allergy, or whether they follow secondary pulmonary congestion, failure of the right ventricle, anoxia, occasionally emphysema and structural abnormalities, such as asthenia, drop-heart, and scoliosis.

Several authors mention cardiac relationship between bronchial asthma and its closely related clinical conditions. The origin of typical electrocardiographic changes was studied by Kállós. In experimental asthma of rabbits, he came to the conclusion that such changes followed myocardial anoxia and reflex coronary spasm leading to functional disorders. Such abnormalities persisted only as long as the asthmatic attack lasted, and structural changes were infrequent. Mainzer, Krause, Harkavy, Romanoff, Urbach, Loew and Gottlieb studied similar conditions in human beings. They found that while myocardial anoxia was present only as long as the attack lasted, varying degrees of defective conduction and functional lesions persisted for days, weeks, and even permanently. This condition is considered to be allergic coronary disease or anoxic myocardial lesion. It may be explained by secondary conditions complicating asthmatic state—infection, increased cardiac strain and excess of drugs. Experiments confirmed this theory, inasmuch as administration of caffeine during artificially established asthmatic attacks induced myocardial lesions (Knepper, Page 1).

Zárdy stated that electrocardiographic changes are due to relative ischemia, meaning that the amount of blood supplying the heart at rest becomes inadequate in excessive strain and stress (relative coronary insufficiency). Such overwork may be established by tachycardia in hyperthyroidism and by administration of epinephrine, i.e., sympathomimetic hormones increasing the  $O_2$  demand of heart-muscle cells. Coronary ischemia may follow allergic inflammatory conditions (focal dis-

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## HEART IN BRONCHIAL ASTHMA—HAJOS

TABLE I. AGE OF PATIENT AT FIRST ASTHMATIC ATTACK

Age	Number of cases
0-15 years	24
16-30 years	92
31-45 years	122
46-60 years	50
61-75 years	13

ease). Excessive administration of epinephrine leads to coronary insufficiency, increasing the blood flow and impeding thrombus formation, and so explaining relative rarity of coronary thrombosis and infarction of asthmatic patients. In our series of 301 cases, we found this condition only once. Excess of epinephrine may produce hemorrhage of the intima leading to coronary apoplexy (Master). Tachycardia in asthma derives from increased excretion and administration of epinephrine. One cause of sudden death in asthmatic individuals is overdosage of epinephrine or morphine; another cause according to Facquet-Claissé, being suffocation. Thus the fatal condition which leads to sudden death in asthma is probably ventricular fibrillation.

K. Hajós emphasized the importance of the asthmatic constitution, as well as the simultaneous occurrence of emphysema and drop-heart associated with the asthenic habitus. Several authors mention drop-heart as an important structural factor, and report special emphysematous electrocardiographic features. Master thought the drop-heart to be due to depression of the diaphragm in emphysema.

Winternitz and Olaf explained increased auricular activity with right axis deviation by right auricular preponderance. Wide, peaked P waves in the second and third leads associated with flattened P waves in the first lead point towards deviation to the right of the P wave axis.

Cooke found elongation of the QS conduction time, splitting of the QS segment and tachycardia to be the characteristic features of the electrocardiographic pattern in bronchial asthma.

In the following review of 301 mainly allergic asthmatic patients I wish to discuss the relationship between electrocardiographic findings and the cardiac state.

In dealing with the heart and circulation we considered the following criteria:

History: (1) age at first asthmatic attack; (2) duration of the asthmatic state at the time of our investigation.

Physical examination: heart size, heart sounds, murmurs, pulse rate, blood pressure, condition of lungs, structural deformities.

X-ray of heart and lungs.

Electrocardiographic findings.

Table I shows that 71.3 per cent of 301 patients developed their first

TABLE II. DURATION OF ASTHMATIC STATE AT TIME OF INVESTIGATION

Years	Number of cases
0-10	192
11-20	71
21-30	28
31-40	8
over 40	2

asthmatic attack between the years of fifteen to forty-five; diagnosis of asthma is more difficult in patients over forty-five years of age because of pulmonary and cardiac involvement. Faragó found that, although there had been no asthmatic symptoms in earlier years, the presence of certain structural deformities, such as drop-heart, had been habitual findings indicating an asthmatic constitution.

Table II shows that in 64 per cent of our cases the asthmatic state had been established approximately four to five years; in twenty-three (6 per cent) from ten to twenty-six years.

The physical examination was normal in 36.6 per cent. Important auscultatory findings were low, dull heart sounds independent of presence or absence of emphysema. Murmurs were less frequently noticed; i. e., an apical systolic murmur had been audible in 8.3 per cent, an aortic systolic murmur in 1 per cent, while an apical diastolic murmur could be heard in only one case. Accentuation of the pulmonary second sound occurred in 4.6 per cent; accentuation of the aortic second sound in 2 per cent.

Changes of pulse rate are significant for bronchial asthma. Tachycardia was noted in 34.6 per cent of our cases (over 100/min.), and only 2 per cent had bradycardia (below 60/min.).

Blood pressure readings showed similar changes. In 48 per cent, we found low systolic pressure (80 to 120), while hypertension had been established in 14.3 per cent (generally in advanced age and with doubtful asthmatic cases). Blood pressure had been physiological in 38 per cent.

Characteristic changes of pulse rate and blood pressure follow the asthmatic state and its treatment (epinephrine-effect). Furthermore, such changes may be stimulated by the asthmatic-asthenic constitution itself. It is well known that allergic reactions are associated with a fall in blood pressure. These symptoms are the result of allergic factors, endocrine function and constitutional disposition, or of the effect of drugs (theophylline, xanthine derivatives, barbituric acids).

In examining the lungs, we found various degrees of emphysema in 61.6 per cent, with associated percussory and auscultatory signs.

Emphysema associated with the asthmatic state may be primary, or it may be a secondary manifestation due to forced expiration. Naturally, emphysema complicates the asthmatic state under all circumstances because

of its influence on the heart and circulation. Acute or chronic cor pulmonale may follow severe cases. Signs of even slight emphysema at the beginning or after short duration of asthma may be detected on the electrocardiogram tracing pointing towards aggravation of symptoms.

In evaluating electrocardiogram tracings we should not forget that however exact this method of investigation may seem, it does not suggest in itself cardiac abnormality. Simultaneous fluoroscopy determines how far these changes follow structural abnormalities or whether they are merely secondary cardiac involvements of the severe asthmatic state.

Correct interpretation of electrocardiogram findings can be realized by the aid of simultaneous x-ray studies. Right axis deviation, inverted T waves, low voltage, changes in the ST segment could easily be taken for myocardial damage, although their only cause may lie in the shape and size of the heart, development of the thoracic cage, and emphysema.

X-ray studies of asthmatic patients confirm frequency of drop-heart with emphysema. We found this combination in 14.3 per cent of our cases without any auricular or ventricular enlargement. Left heart preponderance occurred in 9 per cent and enlargement to the right in only one case. Left ventricular preponderance had been present in 3 per cent, mitral and aortic configuration respectively, on one occasion; horizontally placed heart in 2.6 per cent. Drop-heart generally followed asthenic habitus; aortic configuration was associated with elongation and widening of the aorta. Auscultatory changes of the left side of the heart, particularly left ventricular preponderance, were apical systolic murmurs and accentuation of the pulmonary second sound.

The asthmatic habitus is generally congenital. In advanced age it is difficult to discern whether asthmatic constitution had been established previously to sensitizing factors.

Exact data concerning cardiac conditions could be acquired by autopsy. The difficulty lies in the fact that relatively few die from an acute asthmatic attack, and at autopsy we encountered only secondary asthmatic involvements. In our few autopsied asthmatic cases, we were unable to detect any changes characteristic of the asthmatic state (Radó). We finally came to the conclusion that either a central nervous effect or excess of drugs was responsible for sudden death in asthma, and not allergic reactions of the coronary system, as thought earlier.

Although electrocardiographic investigation gives the most exact solution of definite cardiac and circulatory changes in asthma, it is difficult to determine slight changes. We have to take the patient as a whole and consider the state of heart and circulation during the progress of the disease. We should consider secondary cardiac states responsible for transitory electrocardiographic changes and slight symptoms of no special importance.

Right axis deviation, as mentioned by the great majority of authors, is

one of the principal changes seen in electrocardiographic tracings. Kahn thought it to be due to right ventricular enlargement; Boas and Mann noticed right axis deviation in chronic cor pulmonale; Alexander Luten and Komntz found it without actual cardiac enlargement. Master stated that even in hypertensive patients over fifty years of age, right ventricular enlargement was preponderant.

In our own cases, the following electrocardiographic changes were the most conspicuous:

1. Right axis deviation.
2. Peaked, wide P waves in the second and third lead (P pulmonale, increased right auricular activity).
3. Depression of the ST segment and inverted T waves in the second and third lead.
4. Splitting of R and S waves.

Elongation of the QS conduction time was noteworthy, but was less frequently encountered.

Right axis deviation was well defined in 44.3 per cent of our cases, while left axis deviation was present in only 28.3 per cent; there was no axis deviation in 27.6 per cent.

We came to the conclusion that asthma, in itself, does not change the cardiac configuration, but secondary involvements, such as pulmonary congestion, structural deformities, and associated cardiac disease, are responsible for the enlargement of the conus and pulmonary artery (which Parkinson and Hoyle demonstrated in oblique x-ray views), as well as for right cardiac hypertrophy and right axis deviation. Aortic and mitral configuration are a sequel to valvular disease independent of asthma.

Cardiac enlargement, especially to the left, depended upon the grade of pulmonary involvement. Right cardiac strain in asthma and emphysema established overwork of the whole heart (acute cor pulmonale), and was responsible for changes of the ST segment and T wave.

Among changes in the ST segment, depression is the most frequent, having occurred thirty-eight times in the second, and thirty-one times in the third lead.

Convexity of the ST segment was prominent in forty-one cases in the second, and thirty-three times in the third lead. Depression of the ST segment occurred twenty-three times in the first lead, and convexity fourteen times in the same lead. Depression of the ST segment in the second and third lead was generally associated with inverted or diphasic T waves of the same leads. It seems to be noteworthy that T waves were flattened ninety-three times in the first, and only seventy-four times each in the second and third leads. We found inverted or diphasic T waves in forty-four cases in the third lead, and four times in both the second and third

lead. We must bear in mind that in bronchial asthma flat T waves in the first lead more frequently indicate myocardial damage than the inverted T waves of the third and even second lead.

Although we had to diagnose myocardial lesion in some cases, we should not forget that inverted T waves and depression of the ST segment in the third or even in the second lead are a sequel to high-graded right-axis deviation. Signs indicating coronary insufficiency generally follow local ischemia and do not mean actual coronary lesion, inasmuch as symptoms of the latter condition are usually permanently present, while changes due to the asthmatic state are reversible and disappear with the acute asthmatic attack. We proved the reversibility of asthmatic coronary spasm in our experiments, where five to six minutes after subcutaneous injection of 0.0005 gm. of epinephrine the heretofore inverted T waves became upright.

The QRS segment displayed changes of pattern in our electrocardiographic tracings. We found that partial interventricular block with elongation of the QS conduction time (over 0.09 to 0.10 seconds) in seventeen cases, was generally followed by splitting of the R and S waves in the second and third lead (splitting of the R wave seven times in the third, four times in the second, and once in the first lead). These changes are probably based on secondary right ventricular hypertrophy, which establishes delayed conduction in the interventricular septum. Although complete heart block is rare, we found partial bundle branch block in several instances, right bundle branch block once, left bundle branch block three times, and one case each of Wilson and arborization blocks.

In advanced state of emphysema, T waves become inverted in the second and third lead (right ventricular dilatation and hypertrophy), and right auricular preponderance ensued with large P waves in the same leads. We found peaked, high P waves in 23.3 per cent, even in otherwise low voltage electrocardiographic tracings.

All these changes finally lead to right ventricle failure with pulmonary hypertension. Left axis deviation is always of cardiac origin, such as coronary disease with hypertension and left ventricular enlargement. In one of our cases we found right axis deviation during the first decade of the asthmatic state; when secondary left heart failure had been established, the electrical axis deviated to the left.

We found elongation of the PR conduction time (over 0.20 seconds) based on right auricular preponderance in twelve cases.

Low voltage, as another change of the electrocardiographic pattern, was noticed in 7.3 per cent. As right axis deviation had been generally associated with high voltage, its percentage may be compared with the above-mentioned number.

As to heart rhythm, 94 per cent had normal sinus rhythm, of which 63.6 per cent were of normal frequency; 34.4 per cent had sinus tachycardia, and 2 per cent sinus bradycardia. Abnormalities of rhythm were

present in 6 per cent; seven cases of ventricular, four supraventricular, one auricular and one mixed form of ectopic beats. We found four cases of respiratory arrhythmia, and one with nodal rhythm.

Tachycardia follows the asthmatic state, vasomotor lability, and excess of epinephrine. Tachycardia and pulse pressure may rise to such a degree as to simulate hyperthyroidism. Frequently we encountered increased basal metabolic rate with increased thyroid function.

By means of the electrocardiogram the possibility of myocardial damage was generally excluded and myocardial lesions were found in only 25.3 per cent.

#### SUMMARY

1. Discussion of 301 cases of bronchial asthma with respect to cardiac and circulatory changes associated with structural, pulmonary, and specific asthmatic conditions.

2. Characteristic electrocardiographic tracings in asthma were found to be due to secondary manifestations, and not to special allergic reactions.

3. Abnormalities of heart and circulation meant less frequent actual damage in asthma than in other conditions.

4. The heart may be involved in bronchial asthma to a lesser extent than in associated valvular lesions, although the asthmatic state may aggravate established heart failure.

5. It must be emphasized that, especially in bronchial asthma, the electrocardiogram *per se* cannot give a true picture of the heart, and therefore the entire individual must be taken into consideration.

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Acknowledgement and thanks are extended to Drs. Bien, Gara, László and Radó for their help in taking the electrocardiographic tracings recorded above.

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## NETHAPHYL IN BRONCHIAL ASTHMA

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THE reason for presenting this subject is aptly summarized by Lovelless,<sup>3</sup> who said, "The need is so great for agents which will relieve asthma without the involvement of the hypodermic syringe or complicated inhalation apparatus that any addition to our armamentarium should be welcomed."

In comparison to Hansel's<sup>2</sup> 750 patients, the present series of forty indeed looks small. However, the purpose of this series was not to test the efficacy of Nethaphyl (Merrell) in bronchial asthma *per se* but rather to test its usefulness in asthmatic patients who had been perfectly well satisfied with the temporary relief they obtained with various ephedrine preparations—particularly Tedral and less often Amodrine or capsules of Ephedrine and Amytal.

The Nethaphyl tablets are scored and each contains Nethamine (methylethylaminophenylpropanol) hydrochloride,  $\frac{3}{4}$  gr., and Butaphyllamine (theophylline aminoisobutanol), 2 gr. Nethaphyl with phenobarbital tablets contain, as well, phenobarbital,  $\frac{1}{4}$  gr. to each. The Amodrine tablets (Searle) each contain Racephedrine hydrochloride,  $\frac{3}{8}$  gr., Aminophyllin,  $1\frac{1}{2}$  gr. and phenobarbital,  $\frac{1}{8}$  gr. The Tedral Tablets (Maltine) each contain ephedrine hydrochloride,  $\frac{3}{8}$  gr., theophylline, 2 gr. and phenobarbital,  $\frac{1}{8}$  gr. Ephedrine and Amytal capsules (Lilly) each contain  $\frac{3}{8}$  gr. ephedrine and  $\frac{3}{4}$  gr. amytal. The action of theophylline and aminophylline is well known. Butaphyllamine contains approximately 67 per cent theophylline, is possibly more stable and soluble than similar compounds and in toxicity on the experimental animal compares favorable with aminophylline.<sup>5</sup> Both Racephedrine and Nethamine hydrochloride have essentially the pharmacological action of ephedrine except for producing no noticeable pressor action and minimal central stimulation.<sup>1,4</sup>

Our observations were made on forty middle-aged, male asthmatic patients selected at random from those classified as infectious asthmatic and receiving vaccine therapy. The specific therapy used in these cases will be described later in another paper. All of these patients had been taking Tedral tablets regularly or irregularly for as long as 11 years when they were first referred to us. The first change in regimen was the use of the tablet only when needed (i.e., for definite asthma). Later substitutions were: (1) a capsule containing ephedrine and Amytal, (2) Amodrine tablets, (3) Nethaphyl and (4) Nethaphyl with phenobarbital.

From the Allergy Clinic of Brown General Hospital, Veterans Administration, Dayton, Ohio, and published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

All patients preferred Nethaphyl with phenobarbital over the plain Nethaphyl, due to the added sedative action. Of the forty, one preferred Amodrine to the others, one preferred the capsules containing ephedrine and Amytal, three preferred Tedral tablets and thirty-five preferred or were content with the relief obtained with Nethaphyl with phenobarbital. It is stated "preferred or were content" as these patients were asked if they again wanted ephedrine or were satisfied with the speed and completeness of the relief obtained with Nethaphyl with phenobarbital.

Very few of these patients had seen an allergist prior to being referred to us, and the use of Tedral for asthma has become common among general practitioners. It is not our purpose to condemn any of the ephedrine-containing mixtures. These preparations are useful, effective and dependable, but they have certain disadvantages. First, after some time, frequently the dose must be increased to obtain the same effect—later, a point is reached where satisfactory relief is not obtained regardless of dose. Second, in men of upper middle and old age, ephedrine often, on frequent use, causes a spasm of sphincters, producing a urinary retention. Third, ephedrine increases the blood pressure and pulse rate. Fourth, there is often produced increased nervousness over that already present in asthma, exhibited by a definite tremor of the outstretched fingers.

Discussing this point by point, Nethaphyl also must be increased after being used for some time, but we have found that when ephedrine loses its effectiveness, Nethaphyl gives relief, and *vice versa*, so that with manipulation constant alleviation of asthma may be obtained. No cases of urinary retention occurred while our patients were taking Nethaphyl and those caused by ephedrine definitely diminished. In none of our patients was blood pressure elevated or did tachycardia occur following Nethaphyl. All remarked about the lack of tremor and nervousness and some wondered how they obtained relief without these symptoms. Also there were no toxic manifestations so it was unnecessary to stop the drug in any case for this reason.

Adversely, it must be stated that the action of ephedrine is slightly faster and the relief a bit more complete than with Nethaphyl. Chewing the tablets has hastened the action. Patients, though, prefer Nethaphyl and the somewhat reduced relief, to ephedrine and the side reactions.

Amodrine in our hands did not give adequate relief in most patients though it also did not cause palpitation, tachycardia, rise in blood pressure or nervousness.

#### SUMMARY

1. In a series of forty intrinsically asthmatic patients, thirty-five preferred Nethaphyl with phenobarbital to Amodrine, Tedral or Ephedrine with Amytal.

(Continued on Page 683)

# A CLINICAL EVALUATION OF ORTHOXINE IN THE-TREATMENT OF ALLERGIC DISEASES

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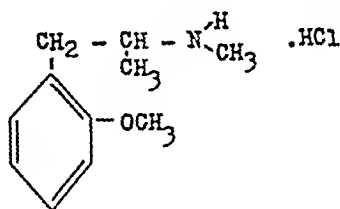
ORTHOXINE is a registered trademark of The Upjohn Company for a new synthetic amine (B-orthomethoxyphenylisopropyl methylamine hydrochloride).

The sympathomimetic amines have found a wide field of usefulness in medicine, particularly in the control of allergic diseases. After the chemical structure of epinephrine was determined, extensive studies on compounds related to it were made.<sup>1,2,5,6</sup> The pioneer investigations of Barger and Dale<sup>3</sup> led to the discovery of many useful compounds and stimulated the great interest in synthetic drugs.

Heretofore the selection of these compounds was based upon the degree of vasopressor activity. Following the discovery of ephedrine, further studies have developed many new and useful therapeutic agents. It is evident that a bronchodilator substance, free from pressor and central nervous stimulation effects, would be valuable for clinical investigation in asthma.<sup>4</sup>

Orthoxine was selected from a considerable number of synthetic amines because when compared to ephedrine sulfate in a large series of animal experiments, Orthoxine has (1) an oral activity comparable to ephedrine, (2) carries no central nervous system excitatory effects, (3) has no pressor action; in fact, appears to be slightly depressor, and (4) exhibits no cardiac effects of altering pulse, either slowing or accelerating.

Orthoxine has the following structural formula:



This is a pure white crystalline substance with a molecular weight of 215.5 and a melting point of 126.5° C. It is soluble in water, alcohol, ether and slightly soluble in ethyl acetate. It is insoluble in petroleum ether, benzene and toluene.

For oral use the salt\* was furnished both as a compressed scored tablet,† 100 mg. (1½ grains) and syrup Orthoxine (each fluid ounce contains 300 mg. or 37.5 mg. (3/5 grains) to the teaspoonful.

\*Supplied through the courtesy of The Upjohn Company.

†Orthoxine tablets are included in the Allergic line of tablets which are formulated to contain excipients, diluents and granulating substances, such as arrowroot starch, cane sugar, and talc, that are less likely to cause allergic reactions than corn starch, lactose and tragacanth, commonly used in tablet manufacture.

One hundred milligram̄s was found to be the average adult dose, although 50 mg. usually served to control the milder symptoms. For children, the syrup was used and one-half to one-teaspoonful according to age was found sufficient. Relief was obtained in twenty to thirty minutes when given orally and lasted from three to four hours. Children five and six years old tolerated teaspoonful doses of the syrup without untoward effect. Of the entire series of 175 patients only two experienced unpleasant effects of nausea and vomiting. Patients were instructed to take the drug when symptoms first were manifest with the exception of the asthmatics who were instructed to take it prophylactically. Only those who followed instructions to omit the so-called antihistamines and sedatives are included in this report. If symptoms became worse, a subcutaneous injection of epinephrine was given and the case was considered a "poor" result.

The majority of patients were receiving specific immunization therapy and all were told that the drug was given to obtain symptomatic relief when necessary. Results were noted by questioning the patients when they reported every five days for their antigen injections; otherwise by telephone or on their next visit.

Results are listed in Table I.

TABLE I. RESULTS OF TREATMENT OF 175 PATIENTS WITH ORTHOXINE

	Results		
	Good	Fair	Poor
Allergic Rhinitis			
Perennial .....	5	10	3
Seasonal .....	30	15	10
Asthma			
Mild .....	11	6	3
Severe .....	3	3	7
Urticaria			
Acute (frequent dosage).....	14	4	2
Chronic .....	1	7	7
Angioneurotic Edema .....	2	3	1
Atopic Dermatitis (relief of pruritus).....	0	8	8
Allergic Headaches .....	6	3	1
(Including Migraine-large doses given early and frequently)			
Obstructive Emphysema .....	1	1	0
(Allergic Bronchitis)			
Total .....	73	60	42

#### COMMENT

Compared with a large series of cases previously treated with ephedrine, those receiving Orthoxine showed a heart rate which was more regular and stronger. Also, no arrhythmias were noted as were occasionally produced by ephedrine. No increase of blood pressure was noted in those receiving Orthoxine, even in the arteriosclerotic patients—in fact, an occasional transient depressor response was noted with flushing in three patients. More favorable results were noted in the mild asthmatic patient than in the seasonal hay fever cases. Five of nine severe asthmatic patients were relieved by 50-100 mg. every three hours. No ill effects were noted when continuing these doses. Results were superior in all cases

## ORTHOXINE IN ALLERGIC DISEASES—WITTICH

to those obtained with ephedrine alone. The absence of nervousness and pressor effects was notably absent.

Gastrointestinal allergy was often alleviated, apparently by relieving smooth muscle spasm. One patient with cardiospasm obtained satisfactory relief by taking 50 mg. one-half hour before eating.

Orthoxine in 100 mg. doses every three hours aborted about two-thirds of allergic headache if taken early. Two cases of migraine were followed by nausea and vomiting. As in asthma, little or no relief was obtained if the attacks were well developed.

### SUMMARY

Orthoxine, like ephedrine, has advantages over ephedrine in that it is not affected by digestion and may be given orally. Its greatest value is as a preventive, and its action is just as prolonged as that of ephedrine. It also possesses the advantage of not causing the unpleasant effects of nervousness and other central nervous system excitatory effects, as well as no distressing pressor symptoms. It is safer to give in the old age group.

The greatest benefits, however, were obtained when used in conjunction with avoidance and immunization measures. When administered in 50-mg. doses one-half hour before a high dose of pollen or inhalant extract, it would permit a higher tolerance dose and compared favorably to the antihistaminic drugs in this respect.

Controls using a combination of Orthoxine with barbiturates of either the short or long acting types gave more satisfactory results than when Orthoxine was administered alone. Such a combination gave considerably better results, but these results are not included in this report since the comparative effect of this synthetic amine with ephedrine alone was desired. Other combinations which have so far given very promising superior results are Orthoxine and a theophylline derivative in combination with an antihistamine and Orthoxine, theophylline derivative, and phenobarbital. Orthoxine alone has been found to be a valuable aid in the treatment of those allergic diseases benefited by ephedrine, with the advantage of being comparatively free from side reactions.

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## CRYMOTHERAPY AND ANAPHYLAXIS

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TEMPLE Fay<sup>1</sup> and his associates in studying refrigeration of humans have shown that the body temperature may be lowered to 31° C. for as long as eight days. The lowest temperature induced by Fay in a human was 23.3° C. Death ensued after four hours. Whittemore<sup>2</sup> and his group, in studying the refrigeration problem in animals, found the respiratory exchange is lowered in hibernating animals, and below 15.5° C. the respiratory quotient may be reduced to as low as 0.51. Similar changes in humans have not been found. In hibernating animals the blood sugar and adrenalin were decreased. In humans under refrigeration there are no significant changes in blood urea, nonprotein nitrogen, cholesterol, sugar, chlorides, calcium, phosphorus, or CO<sub>2</sub> combining power. A significant observation in hibernating animals was the definite lowering of the basal metabolic rate. In refrigerated humans a lowering of the basal metabolic rate was also observed.

The observations of a decreased metabolism suggested that various undetermined physiologic processes were slowed up, if not actually suspended. It occurred to the author that use of refrigeration might possibly slow up or suspend the antigen-antibody reaction of anaphylaxis or possibly affect the action of histamine on the bronchial musculature of guinea pigs. Two interesting experiments sustained these possibilities. Taintor is quoted by Whittemore as having found that toxic dinitrophenol injected into guinea pigs and pigeons failed to produce the usual stimulation if environmental temperature was 38° to 42° F., and only 25 per cent of the birds died. Toshivo Akiyama is also mentioned by Whittemore as having inoculated ground squirrels with the virus of lymphogranuloma inguinale and then put them into hibernation. Those which hibernated for twenty days remained unharmed without signs of the disease. The controls, not hibernated, died.

Twenty guinea pigs of average 300 gm. weight were sensitized by an intra-abdominal injection of 1 c.c. of a 1:10 dilution of horse serum. After fourteen days, the animals were refrigerated. Since this was in the nature of a preliminary experiment, a simple technique of tying down the four limbs of an animal to a base board and packing ice about it was used. A thermometer was kept fixed in the rectum of each animal. Temperatures dropped from 38° C. to 25° C. within a matter of thirty minutes. No anesthetic to make induction of refrigeration easier was used. Since the room temperature usually ranged from 14° to 20° C., when the induced temperature reached 25° C., the ice was removed from the guinea pigs. Their temperatures drifted slowly downward, and often it was necessary to reheat the animals to prevent it from falling too low.

Of the twenty animals thus refrigerated, seven died from the procedure

because the temperature had been deliberately lowered dangerously to between 16° and 20° C., with the intention of observing the effects of extremely low temperatures. It may be stated that at 25° C. the animal may easily be restored, by reheating with a heating pad, and returned to normal life. Autopsy findings on animals dying from lowered temperatures revealed that refrigeration induced extreme distention of the entire gastrointestinal tract, including the gall bladder. The liver was also enormously enlarged and showed passive congestion. The lungs were small and pink, except in those cases refrigerated for several hours, in which passive congestion was present with isolated hemorrhagic areas on the surface. The auricles and tributary veins were moderately engorged. The over-all heart size seemed normal.

The actual test animals were refrigerated at temperatures ranging from 18° to 27° C. for periods varying from sixty to 195 minutes, after which time they received an intravenous injection of 1 c.c. of a 1:2 dilution of horse serum. Of the thirteen animals who survived refrigeration, only five survived fatal anaphylactic shock, and all of these animals showed signs of anaphylaxis. Fatal shock was confirmed by autopsy findings. Due to the relatively inactive condition of the animals under refrigeration, the only dependable sign of anaphylaxis was severe dyspnea. Shivering, followed by clonic-like movements of the limbs and accompanied by rapid, shallow breathing, was observed during the process of refrigeration. Ten control animals, not refrigerated, died from fatal anaphylaxis after the same shock dose.

Refrigeration seemed to produce an unusual condition in guinea pigs, with respect to anaphylaxis, which neither histaminase, histamine, papaverine nor crotalin<sup>2,3,4</sup> had produced. It definitely seemed to lengthen the time interval between the injection of the shock dose of antigen and the onset of anaphylactic dyspnea. This retarding of the effects of the immunological reaction could have taken place at several possible points. The circulation time might have been slowed so that the antigen reached the site of the shock organ slowly; or the reaction between antigen and antibody might have been slowed; or after the said reaction, the release of histamine from the cells might have been slowed; or, lastly, the action of released histamine on bronchial musculature might have been delayed. Thus far, it has been convenient to test only one of these possibilities, the last. For this, five guinea pigs, refrigerated from sixty to 200 minutes, were injected intravenously with histamine in a dose of .045 mg. per 100 gm. weight. All five died in shock but after a lapse of six to nine and one-half minutes. Signs of dyspnea were delayed three to five minutes in starting. In fatal histamine shock, dyspnea sets in usually in fifteen to sixty seconds. The delay in onset of symptoms due to the action of histamine seems significant and is apparently attributable to the slowing of some physiological processes as a result of refrigeration.

*(Continued on Page 704)*

# THE INTEGRATION OF THE PRACTICE OF ALLERGY AND PSYCHIATRY

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PSYCHOSOMATIC medicine has become of increasing interest and importance in the past few years, as evidenced by the vast literature and by the popularity of symposia on this subject.

Recently, The American College of Allergists conducted a forum on "Psychodynamics and the Allergic Patient,"\* indicating the progress made in both fields—the allergist becoming aware of the importance of the psychiatric approach to some of his problems, and the psychiatrist in turn coming around to the view that, although he could be of help to the allergist, allergy was not *exclusively* within his domain. In the past, it is to be regretted, some rash psychiatrists had expounded views indicating that asthma, hay fever, urticaria, and other allergic diseases were primarily psychosomatic disorders, denying hypersensitivity, the basis of allergy. Now we are agreed that both the allergist and the psychiatrist can jointly contribute to the solution of some problems seen by the allergist.

Allergy and psychiatry have a great deal in common. Both are new disciplines in the practice of medicine, and as such are not completely accepted in certain medical circles who deny the role of either allergens or emotions in the production of disease.

Both the allergist and psychiatrist are essentially medical detectives; they search for hidden causes. The allergist looks for specific allergens and resorts to his special techniques of skin-testing, food diaries, elimination diets, et cetera. The psychiatrist probes the unconscious mind with his special technique of psychoanalysis in order to uncover hidden emotional factors producing symptoms.

The two disciplines treat primarily with disturbances in *function* although organic disease is encompassed within the boundaries of both allergy and psychiatry. The underlying mechanism in an allergic reaction, according to present theory, is based on a specific antigen-antibody reaction, resulting in the release of histamine or a histamine-like substance in a hypersensitive individual. Comparably, emotional disorder, according to Freudian concepts, is produced between the interaction of the Ego and the Id in a susceptible individual, and may manifest itself in organ reaction, producing symptoms.

In allergy, the skin is frequently the "bookkeeper of the body," record-

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Based upon an address delivered as part of a symposium on psychosomatic medicine, held under the auspices of the Department of Psychiatry, New York Medical College, Flower-Fifth Avenue Hospital, New York, N. Y., June 12, 1947.

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\*Third annual session, the American College of Allergists, June 7, 1947, Atlantic City, N. J.



ing experiences (exposures to specific allergens) of the past. It records sensitivity which may have been acquired years ago and which may be revealed by skin-testing. This is comparable to the indelible recording of certain emotional experiences within the recesses of the unconscious mind—experiences which, considerably later, may generate symptoms. There is a type of "sensitization" in both instances. Embryologically, it must be recalled, the skin and brain have a common origin, the ectoderm.

Another phenomenon common to allergy and psychiatry is that exposure to relatively innocuous substances or situations may result in explosive reactions in these "sensitized" individuals. Thus, the anaphylactic type of reaction which may follow the ingestion of milk or aspirin may be comparable to the induction of an acute psychosis by some mild mental trauma or frustration. A fertile field or "sensitivity" is necessary in both instances. Sometimes, these reactions are mild but continuous, resulting in chronic irritation and disability. At times, the reaction is delayed following exposure, a period of "incubation" being needed before the production of mental or allergic symptoms. At other times, an initial exposure to a harmful allergen or experience results in a series of "chain reactions"—an imbalance is created which may enhance and multiply the "sensitivities" of the allergic or psychiatric patient.

In the therapeutic approach to the patient, there is much in common between the allergist and the psychiatrist. We both seek "cures" by searching for and removing specific offenders, whether it be a specific allergen in the form of a cat or canary, or a specific fixed idea or situation causing emotional disturbances. Failing such "cures," we both resort to "desensitization"—the allergist by injection with specific antigens, and the psychiatrist by psychotherapy.

The fact that the emotions can produce symptoms, often mistaken for organic disease, is now generally accepted, and we must be grateful to those keen observers (internists and psychiatrists) who have reawakened our interest in an old subject, newly named psychosomatic medicine.

Undoubtedly, the allergist can learn much from the psychiatrist, who is a specialist in the art of history-taking. An accurate and detailed history can be more important to the allergist than skin-testing. Furthermore, the emphasis of psychiatry upon the consideration of the *individual as a whole* in a *specific environment* (as though he were bathed in a sea of stimuli, emotional and otherwise) merits emulation by the allergist. Without such a broad consideration, one treats symptoms out of context, a narrow and limited view frequently leading to failure. In the opinion of Nardo,<sup>†</sup> such a limited view results in the practice of "veterinary medicine."

The allergist might heed as well the injunction of Weiss<sup>‡</sup>: "to consider not only what the patient 'et' but whom he may have met."

The allergist is aware of the fact that asthma itself, regardless of

<sup>†</sup>Discussion of Harold A. Abramson's paper on: "Psychodynamics and the Allergic Patient."

cause, may produce a neurosis in the patient. The sufferer from asthma, during an attack, frequently fears impending death and develops phobias as a result of this experience. This has been labeled by Sarah Jordan as a "somatopsychic" manifestation in contrast to psychosomatic phenomena. What the allergist frequently overlooks, however, is the fact that once asthma supervenes, though it may have been strictly allergic in origin, it may *recur* on a psychogenic basis. Thus, the youngster who has asthma from the ingestion of specific foods may precipitate an attack just before leaving for school because he does not like his teacher, or because he wants (and needs!) the attention of an errant mother. Failure of the allergist to recognize this aspect of his practice will result in failure of therapy, regardless of dietary restrictions, environmental cleansing, and injections. The allergist should be cautioned, however, of the danger of so emphasizing the psychogenic factors as to overlook completely the cat or canary, whose removal may relieve the patient.

When the allergist is aware of the psychosomatic aspect of illness, he is frequently uncertain as to when the psychiatrist need be consulted. Moreover, when he does feel the need for psychiatric help, he is often deterred from such consultation because of the prohibitive cost in both time and money—assuming he has convinced the patient of the advisability of such a procedure, which is frequently an impossibility.

It, therefore, behooves the psychiatrist to teach us to recognize psychogenic factors, to determine when the special techniques of psychiatry are indicated and, above all, to simplify and shorten the methods of analysis and therapy so that it comes within the bounds of the average patient.

When the allergist and the psychiatrist forget the "either or" concept and, instead of being at loggerheads, join co-operatively to treat patients, then progress will surely have been made—to the benefit of both doctor and patient.

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Dr. Bernard N. Halpern, Paris, France, the Lauréat of the Institute and Académie of Medicine, Chief of Laboratories of the Faculté of Medicine and Chief of Research of the National Center of Scientific Research, has joined the Editorial Board of the *International Archives of Allergy and Applied Immunology*, the official organ of the International Association of Allergists, Inc.

## RELIEF OF ASTHMA BY MEANS OF LOW MELTING POINT SUPPOSITORIES

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**A**N asthmatic suffering from an acute paroxysm desires speedy relief. In proven cases, the self-administration of certain drugs such as 1:100 epinephrine hydrochloride, glycerinized or unglycerinized, via oral inhalation; the use of ephedrine or aminophylline, et cetera, orally, and the use of aminophylline in solution or aminophylline suppositories intrarectally can safely be recommended.

Aminophylline is rapidly absorbed from the mucosa of the lower intestine through the portal system. If the drug is given in solution according to the method described by Barach,<sup>2</sup> absorption takes place rapidly. Relaxation of the smooth muscles of the bronchi takes place, and, in most instances, the patient secures the desired relief.

The use of aminophylline hypodermically or by catheter usually requires the presence of a physician or nurse. Suppositories containing aminophylline in combination with other drugs can easily be self-administered.

Practically all of the commercial aminophylline suppositories in use at the present time have a base with a high melting point. This delays absorption of the drugs incorporated in the suppository base. Bowel movements are often produced by the pressure and hygroscopic action of the suppository in the rectum.

A burning and painful sensation is also produced when aminophylline suppositories are used, even though various local anesthetics are incorporated into the base of the suppositories.

During the 1945 Fall Instructional Course of the American College of Allergists,<sup>1</sup> the formulas of a number of low melting point suppositories that have been in use at the Lancaster General Hospital during the last five years were submitted and are listed as follows:

### No. 1

Aminophyllin gr. vi  
Ephedrine sulphate gr. 3/8  
Phenobarbital gr. i  
Nupercaine qs. 1 per cent  
Peanut oil, spermaceti and oleum theobromitas in equal parts to make one suppository.

### No. 2

Aminophyllin gr. vi  
Sodium Pentobarbital gr. iii  
Nupercaine qs. 1 per cent  
Peanut oil, spermaceti and oleum theobromitas in equal parts to make one suppository.

<sup>1</sup>Presented at the annual meeting of The American College of Allergists, Atlantic City, New Jersey, June 7, 1947.

## No. 3

Aminophyllin gr. vi  
 Ephedrine sulphate gr. ss  
 Sodium Pentobarbital gr. iss  
 Nupercaine qs. 1 per cent  
 Peanut oil, spermaceti and oleum theobromitas qs. one suppository

## No. 4

Aminophyllin gr. vi  
 Ephedrine sulphate gr. ss  
 Demerol, 50 milligrams  
 No anesthetic  
 Peanut oil, spermaceti and oleum theobromitas to make one suppository.

The suppository base used in the formulas was originated by two Lancaster pharmacists.\* Only two cases in which an untoward reaction had been produced by the use of one of the suppositories have been noted

## CASE REPORTS

Case 1.—Sister E. A., a nun, aged twenty-six, a hay-fever sufferer and pollen asthmatic, was given the following prescription:

Aminophyllin gr. vi  
 Sodium Pentobarbital gr. iss  
 Nupercaine qs. 1 per cent  
 Peanut oil, spermaceti and oleum theobromitas qs. one suppository.  
 Misce: XII suppositories.  
 Signa: Insert one into rectum before retiring for relief of nocturnal attacks.

Sister E. developed a rather severe edema of the anal area plus severe itching after the use of one of these suppositories. She later was proved to be sensitive to coca butter.

Case 2.—Another patient developed a generalized urticaria after using several of the following suppositories:

Aminophyllin gr. vi  
 Ephedrine sulphate gr. ss  
 Sodium Pentobarbital gr. iss  
 Nupercaine qs. 1 per cent  
 Peanut oil, spermaceti and oleum theobromitas qs. one suppository.

The cause of the urticaria was not determined since the patient did not return for testing. One of the following ingredients was probably responsible: peanut oil, coca butter, nupercaine or sodium pentobarbital. No one sensitive to spermaceti has been discovered by the writer. As far as is known, none have been described or listed in the pertinent literature.

The loss of popularity of medications administered via suppositories can be attributed to three factors:

1. Lack of certainty with regard to dosage.
2. Slow absorption due to high melting point base.
3. Allergy to the base.

Since the suitability of the mucous surface of the bowel for prompt absorption of the drugs has been well established,<sup>4,5</sup> the marked decrease in effectiveness of drugs so administered must be due to the influence of the suppository base, or to a sensitivity to one of the ingredients in the base of the medications incorporated therein. The need for a sup-

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pository base which would not contain coca butter or peanut oil and still have a low melting point has been known for some time.

Data from recent studies indicate that fatty bases have a deleterious influence on absorption and availability of both oil and water soluble drugs.<sup>3,4</sup> This may be overcome by the addition of a suitable emulsifying agent.

Spermaceti was selected with these facts in mind. It consists chiefly of cetyl palmitate, cetyl alcohol in appreciable amounts and small amounts of the esters of lauric acid, stearic and myristic acids. Cetyl alcohol itself is a good emulsifying agent.

The melting point of spermaceti is 42° to 50° C. The addition of liquid petrolatum and white petrolatum to lower the melting point and still leave a solid medication was undertaken. The following is the finished suppository base:

Petrolatum liquid	42.
Spermaceti	45.
Petrolatum alba	13.
	<hr/>
	100.

If a more solid medium with a slightly higher melting point is desired, it can be obtained by increasing the amount of spermaceti and by decreasing the amounts of petrolatum. The formulas in use at the present are made as follows:

*No. 1*

Aminophyllin gr. vi  
Ephedrine sulphate gr. 3/8  
Phenobarbital gr. i  
Nupercaine qs. 1 per cent  
Base qs. one suppository.

*No. 2*

Aminophyllin gr. vi  
Sodium Pentobarbital gr. iss to gr. iii  
Nupercaine qs. 1 per cent  
Base qs. one suppository.

*No. 3*

Aminophyllin gr. vi  
Ephedrine sulphate gr. ss  
Sodium Pentobarbital gr. iss  
Nupercaine qs. 1 per cent  
Base qs. one suppository.

*No. 4*

Aminophyllin gr. vi  
Ephedrine sulphate gr. ss  
Demerol, 50 milligrams  
Base qs. one suppository.

The base melts rapidly at body temperature, and the absorption of the drugs incorporated therein takes place rapidly. Self-administration of the suppository can safely be recommended. They can be used to control attacks of asthma, to relieve nocturnal attacks and to provide the relaxation that an asthmatic patient requires to secure an adequate amount of sleep.

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# ASYMPTOMATIC EOSINOPHILIA FOLLOWING PENICILLIN ADMINISTRATION

## Report of a Case

By MORTON S. BERK, M.D., and S. BERTRAM SOSTEK, M.D.

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ALTHOUGH reactions to crystalline penicillin of allergic nature have been frequently reported since this drug first came into common therapeutic use,<sup>9,11,13</sup> the presence of eosinophilia has only infrequently been noted to accompany such reactions.<sup>4,12,13</sup> Eosinophilia without any other manifestation of hypersensitivity to penicillin has never been previously noted in the literature, however. This prompted the report of such a case.

### CASE REPORT

E. L., a seventy-three-year-old white widowed woman entered the hospital on May 30, 1946. She had been apparently in subjective good health until one week prior to admission, when pain was noted in the right upper quadrant of the abdomen, radiating to the tip of the right shoulder and aggravated by cough and deep breathing. Following this, the patient became weak, listless and anorexic, and vomited green material on several occasions. Because of persistence of symptoms, admission to the hospital was sought. Past and family histories were noncontributory.

Physical examination revealed an obese, elderly, white woman lying semi-recumbent in bed and breathing dyspneically. Temperature was 100° by mouth, pulse 96, and respiration 32 per minute. Neck veins were moderately distended. The heart was enlarged 2 cm. to the left of the mid-clavicular line. Rhythm was regular, and the rate was 96. A rough, grade 2, aortic systolic murmur, transmitted to the cardiac apex and into the neck, was audible. Examination of the lungs revealed moderate dullness, bronchovesicular breath sounds and crepitant râles at the right lung base. Medium moist râles were present at the left lung base. Blood pressure was 140/80. The physical examination was otherwise negative, with the abdomen revealing no abnormal masses or tenderness. X-ray examination of the chest revealed marked cardiac enlargement, hypertensive in type, with calcification of the aortic arch and bilateral congestive changes. At the right lung base there was an area of infiltration, and fluid was present in the septum between the right middle and lower lobes. Therapy consisted of digitalization and crystalline sodium penicillin, the latter in doses of 20,000 units every three hours. The white blood count was 7,200, with 76 per cent segmented neutrophils and 24 per cent lymphocytes.

On the second hospital day, the patient's temperature rose to 102.4° F. by mouth, and because of continued nausea and occasional vomiting, subcutaneous clyses were begun. During the following day, however, the patient began to improve gradually. Her temperature gradually diminished until the eighth hospital day, when it reached normal. Two days later, however, the patient again became dyspneic and her temperature rose to 101.5° F. by mouth. Examination of the chest at that time revealed flatness and markedly diminished to absent breath sounds at the right lung base. An x-ray taken at that time revealed homogeneous obliteration of the right lower lung field, interpreted as fluid. Thoracentesis yielded 500 c.c. of cloudy straw-colored fluid, which clotted shortly after withdrawal and

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had a specific gravity of 1.018. Crystalline sodium penicillin, 60,000 units in 20 c.c. of saline, were instilled at the site of the thoracentesis. Cultures of the fluid were negative as was the guinea pig inoculation. Thoracentesis was repeated one week later, but only 20 c.c. of fluid were obtained; 60,000 units of penicillin were again instilled at the site of the thoracentesis.

On continued intramuscular penicillin therapy, the patient's temperature continued elevated for the following three weeks, and she continued anorexic and moderately dyspneic. The white blood count (June 24) was 5,300, with 85 per cent neutrophils and 15 per cent lymphocytes. Early in July, five weeks after entry, the patient's temperature gradually fell to normal, where it remained throughout the remainder of her hospital stay. Despite reversion of the temperature to normal, a dullness to flatness, with markedly diminished breath sounds, continued at the right base. On July 25, 1946, eight weeks after admission the white blood count was noted to be 14,500, with 52 per cent neutrophils, 30 per cent lymphocytes and 18 per cent eosinophiles. On the following day, differential white blood count revealed 28 per cent eosinophiles, and a total eosinophile count was 1,890 per cubic millimeter. At this point the penicillin was discontinued, and one week later the white count was 6,300, with 4 per cent eosinophiles. At this time stool examinations revealed no ova or parasites, and a trichina skin test was negative. Other medications being administered at the time were digitalis, niacinamide, cevitamic acid, Brewer's yeast, and thiamine hydrochloride.

Three days after the reversion of the white blood count to normal, on August 5, the patient was again given 20,000 units of crystalline sodium penicillin every three hours intramuscularly for a period of three days. The white blood count on August 6 was 8,400, with 3 per cent eosinophiles, and on August 8 it was 12,000, with 1 per cent eosinophiles. On August 11, six days after penicillin had been recommenced, and three days after it had been discontinued for the second time, the white blood count was 9,500, with 14 per cent eosinophiles. Total eosinophile count at this time was 1,710 per cubic millimeter. The eosinophile count then fell gradually until August 21, when it was 2 per cent of 8,200 white blood cells. At this time an intradermal skin test with 0.1 c.c. of sodium penicillin, 10,000 units per c.c., gave a positive tuberculin-type reaction which appeared in twenty-four hours and faded in one week. On October 10, 1946, shortly before discharge from the hospital, the patient was given 10,000 units of crystalline sodium penicillin intramuscularly four times daily. On commencing penicillin administration, the white blood count was 8,500, with 1 per cent eosinophiles. Two days later, it was 9,200 with 21 per cent eosinophiles. Eight days after penicillin had been discontinued, the white blood count was 8,000 with 6 per cent eosinophiles. At no time during any course of penicillin administration did the patient show skin lesions of any type. Different lots of penicillin were used throughout the testing, thereby eliminating the factor of a common contaminant in the drug.

#### DISCUSSION

The case reported first developed an eosinophilia following eight weeks of almost constant intramuscular administration of crystalline sodium penicillin. Other common causes for eosinophilia could not be found, and one week after the withdrawal of penicillin the eosinophile count had reverted to normal. Later in the patient's hospital stay, the eosinophilia was reproduced on two occasions. The first was six days following the administration of 20,000 units of crystalline sodium penicillin every three hours. The second reproduction of eosinophilia occurred two days following the intramuscular administration of 10,000 units of penicillin four

times daily. An intracutaneous skin test with crystalline sodium penicillin gave a positive tuberculin-type skin reaction in twenty-four hours, with fading in one week.

In 1943, Lyons<sup>10</sup> noted that eosinophilia of 20 to 30 per cent often occurred following the use of penicillin. At that time it was felt that most of these reactions were probably due to impurities and could be prevented by Seitz filtration of the solution before injection. Since crystalline sodium penicillin has come into common use, there have been only a few other reports of a significant eosinophilia following penicillin administration.<sup>4,12,13</sup> It thus seemed that Lyon's assumption of impurities as the cause of the occurrence of eosinophilia in the high percentages he noted, was, for the most part, true. However, during the past year, reports of eosinophilia accompanying other manifestations of hypersensitivity due to crystalline penicillin have appeared with increasing frequency. Almost all occur in combination with skin lesions. These allergic phenomena have varied from mild skin reactions to severe cases of bullous dermatitis.

The reactions of patients to penicillin have been studied by numerous investigators. Crip<sup>5</sup> demonstrated positive direct and passive transfer tests to penicillin in a patient who developed urticaria following the first injection in a second course of treatment. He concluded that the sensitivity was due to penicillin itself rather than to any contaminating impurities. Lamb<sup>9</sup> believes that the allergenic principle in penicillin is in all probability a polysaccharide fraction. He quotes Jadassohn, Schaaf, and Sulzberger,<sup>8</sup> who found that the products of fungi could produce anaphylactic shock in guinea pigs. These observers also noted that pathogenic fungi contain not only a specific antigen but also another antigen common to all fungi. Price<sup>14</sup> feels that hypersensitivity to penicillin requires an allergen other than penicillin alone. He presumes that the patient's own serum provides the necessary protein. Welch and Rostenberg<sup>18</sup> demonstrated an intense tuberculin-type reaction from intracutaneous tests with penicillin. They state that approximately 5 per cent of 140 previously unexposed persons exhibited a tuberculin-type reaction to the initial injection of crystalline sodium penicillin. Cornia, Jacobsen, and Smith<sup>4</sup> feel that such reactions stem from previous sensitivity to allergenically similar fungi. Feinberg<sup>6</sup> is of similar opinion, stating that early reactions to a first exposure to penicillin are probably due to previous fungus disease, whereas delayed reactions are indications of sensitization development which also may be enhanced by previous fungus disease.

The presence of eosinophiles in increased numbers in the blood stream has been reviewed by Stickney and Heck.<sup>17</sup> These authors note that most experimental studies on the origin of the eosinophilia or the granules of the eosinophilic leukocyte point to the importance of anaphylaxis. Eosinophilia is a common finding in (1) asthma, hay fever and vasomotor rhinitis; (2) parasitic infection, particularly of the intestines; (3)



had a specific gravity of 1.018. Crystalline sodium penicillin, 60,000 units in 20 c.c. of saline, were instilled at the site of the thoracentesis. Cultures of the fluid were negative as was the guinea pig inoculation. Thoracentesis was repeated one week later, but only 20 c.c. of fluid were obtained; 60,000 units of penicillin were again instilled at the site of the thoracentesis.

On continued intramuscular penicillin therapy, the patient's temperature continued elevated for the following three weeks, and she continued anorexic and moderately dyspneic. The white blood count (June 24) was 5,300, with 85 per cent neutrophils and 15 per cent lymphocytes. Early in July, five weeks after entry, the patient's temperature gradually fell to normal, where it remained throughout the remainder of her hospital stay. Despite reversion of the temperature to normal, a dullness to flatness, with markedly diminished breath sounds, continued at the right base. On July 25, 1946, eight weeks after admission the white blood count was noted to be 14,500, with 52 per cent neutrophils, 30 per cent lymphocytes and 18 per cent eosinophiles. On the following day, differential white blood count revealed 28 per cent eosinophiles, and a total eosinophile count was 1,890 per cubic millimeter. At this point the penicillin was discontinued, and one week later the white count was 6,300, with 4 per cent eosinophiles. At this time stool examinations revealed no ova or parasites, and a trichina skin test was negative. Other medications being administered at the time were digitalis, niacinamide, cevitamic acid, Brewer's yeast, and thiamine hydrochloride.

Three days after the reversion of the white blood count to normal, on August 5, the patient was again given 20,000 units of crystalline sodium penicillin every three hours intramuscularly for a period of three days. The white blood count on August 6 was 8,400, with 3 per cent eosinophiles, and on August 8 it was 12,000, with 1 per cent eosinophiles. On August 11, six days after penicillin had been recommenced, and three days after it had been discontinued for the second time, the white blood count was 9,500, with 14 per cent eosinophiles. Total eosinophile count at this time was 1,710 per cubic millimeter. The eosinophile count then fell gradually until August 21, when it was 2 per cent of 8,200 white blood cells. At this time an intradermal skin test with 0.1 c.c. of sodium penicillin, 10,000 units per c.c., gave a positive tuberculin-type reaction which appeared in twenty-four hours and faded in one week. On October 10, 1946, shortly before discharge from the hospital, the patient was given 10,000 units of crystalline sodium penicillin intramuscularly four times daily. On commencing penicillin administration, the white blood count was 8,500, with 1 per cent eosinophiles. Two days later, it was 9,200 with 21 per cent eosinophiles. Eight days after penicillin had been discontinued, the white blood count was 8,000 with 6 per cent eosinophiles. At no time during any course of penicillin administration did the patient show skin lesions of any type. Different lots of penicillin were used throughout the testing, thereby eliminating the factor of a common contaminant in the drug.

#### DISCUSSION

The case reported first developed an eosinophilia following eight weeks of almost constant intramuscular administration of crystalline sodium penicillin. Other common causes for eosinophilia could not be found, and one week after the withdrawal of penicillin the eosinophile count had reverted to normal. Later in the patient's hospital stay, the eosinophilia was reproduced on two occasions. The first was six days following the administration of 20,000 units of crystalline sodium penicillin every three hours. The second reproduction of eosinophilia occurred two days following the intramuscular administration of 10,000 units of penicillin four

times daily. An intracutaneous skin test with crystalline sodium penicillin gave a positive tuberculin-type skin reaction in twenty-four hours, with fading in one week.

In 1943, Lyons<sup>10</sup> noted that eosinophilia of 20 to 30 per cent often occurred following the use of penicillin. At that time it was felt that most of these reactions were probably due to impurities and could be prevented by Seitz filtration of the solution before injection. Since crystalline sodium penicillin has come into common use, there have been only a few other reports of a significant eosinophilia following penicillin administration.<sup>4,12,13</sup> It thus seemed that Lyon's assumption of impurities as the cause of the occurrence of eosinophilia in the high percentages he noted, was, for the most part, true. However, during the past year, reports of eosinophilia accompanying other manifestations of hypersensitivity due to crystalline penicillin have appeared with increasing frequency. Almost all occur in combination with skin lesions. These allergic phenomena have varied from mild skin reactions to severe cases of bullous dermatitis.

The reactions of patients to penicillin have been studied by numerous investigators. Criepe<sup>5</sup> demonstrated positive direct and passive transfer tests to penicillin in a patient who developed urticaria following the first injection in a second course of treatment. He concluded that the sensitivity was due to penicillin itself rather than to any contaminating impurities. Lamb<sup>9</sup> believes that the allergenic principle in penicillin is in all probability a polysaccharide fraction. He quotes Jadassohn, Schaaf, and Sulzberger,<sup>8</sup> who found that the products of fungi could produce anaphylactic shock in guinea pigs. These observers also noted that pathogenic fungi contain not only a specific antigen but also another antigen common to all fungi. Price<sup>14</sup> feels that hypersensitivity to penicillin requires an allergen other than penicillin alone. He presumes that the patient's own serum provides the necessary protein. Welch and Rostenberg<sup>18</sup> demonstrated an intense tuberculin-type reaction from intracutaneous tests with penicillin. They state that approximately 5 per cent of 140 previously unexposed persons exhibited a tuberculin-type reaction to the initial injection of crystalline sodium penicillin. Cormia, Jacobsen, and Smith<sup>4</sup> feel that such reactions stem from previous sensitivity to allergenically similar fungi. Feinberg<sup>6</sup> is of similar opinion, stating that early reactions to a first exposure to penicillin are probably due to previous fungus disease, whereas delayed reactions are indications of sensitization development which also may be enhanced by previous fungus disease.

The presence of eosinophiles in increased numbers in the blood stream has been reviewed by Stickney and Heck.<sup>17</sup> These authors note that most experimental studies on the origin of the eosinophilia or the granules of the eosinophilic leukocyte point to the importance of anaphylaxis. Eosinophilia is a common finding in (1) asthma, hay fever and vasomotor rhinitis; (2) parasitic infection, particularly of the intestines; (3)

dermatoses, especially of the allergic type, and (4) blood dyscrasias and lymphoblastoma. To these causes may be added the administration of medications such as atabrine<sup>16</sup> and liver extract,<sup>7</sup> and less common entities such as Loeffler's syndrome and periarteritis nodosa.

The possible relationship of the eosinophile to blood histamine content and the clinical signs of allergy has been a controversial point. Code<sup>1,2</sup> found that the white cell layer in sedimented blood contained almost 90 per cent of the histamine content of the whole blood when compared with plasma and red cells. During anaphylactic shock, this observer found that the histamine values rose three to nine times in shocked animals, the escape of histamine taking place in the white cell, chiefly from the eosinophiles. He, therefore, concluded<sup>3</sup> that histamine released during anaphylactic shock was an important factor in producing the symptoms and pathologic changes in the reaction. Randolph and Rackman<sup>15</sup> likewise noted that during paroxysms of bronchial asthma in a group of nine cases, elevated blood histamine levels occurred, as compared with quiescent periods. However, they found that in another series of eight cases of eosinophilia of varying etiology, only two cases had elevated blood histamine values. From these studies, it would appear that blood histamine undergoes a definite increase during acute manifestations of hypersensitivity, but that the relationship of blood eosinophiles to histamine is as yet unproven although suggestive.

Thus, the finding of isolated, reproducible eosinophilia in this case is in all probability a manifestation of allergy to crystalline sodium penicillin.

#### SUMMARY

1. A case of asymptomatic eosinophilia due to the administration of crystalline sodium penicillin is presented.

2. The eosinophilia occurred after continuous administration of the drug over an eight-week period. Following discontinuance of the drug, the eosinophilia disappeared, but it was later reproduced on two occasions by administering penicillin for short courses.

3. Intracutaneous administration of a solution of crystalline sodium penicillin caused a tuberculin-type reaction.

4. The relation of penicillin reactions to hypersensitivity is discussed, as is that of eosinophilia and hypersensitivity.

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## THE TOPICAL APPLICATION OF THEPHORIN IN PRURITIC DERMATOSES

(Continued from Page 644)

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# DERMATITIS CAUSED BY ELECTRODE JELLY

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THIS is a case report of dermatitis caused by electrode jelly. To my knowledge this is the first case to be reported. That this condition is rare is proven by the fact that at the Electrocardiography Department of the Veterans Administration Hospital at Hines, Illinois, where about 14,000 electrocardiographic examinations were performed during the past twelve months, no known sensitivity to the jelly was reported.

## CASE REPORT

In January, 1943, while R. C., a white man, aged forty-two, was hospitalized in the Canadian Naval Hospital in St. John, N. F., an electrocardiogram was done. Shortly after the examination, he noticed a redness with slight swelling at the site of the application of the electrode jelly. Within twenty-four hours a pin-point rash appeared at the sites, the swelling increased, and in two days the areas assumed a hemorrhagic appearance. The rash gradually dried up and disappeared within twenty-five to thirty days without any desquamation.

On February 28, 1947, he was called to the Veterans Administration Out-Patient Department for an examination and electrocardiogram. At the completion of the test a rash again appeared at the site of the application of the electrode jelly.

Examination of the rash at that time revealed a finely papular erythematous patch of irregular outline on both forearms (Fig. 1). There was a profusion of discrete, pinhead-sized, pale erythematous papules on the volar aspects of both forearms from the antecubital areas to the wrists, and a moderate number on the antero-medial aspect of the proximal half of the lower half of the left leg (Fig. 2). There was also a profusion of discrete pinhead, erythematous papules over an area of about 6 inches square on the left chest (Fig. 3).

Within forty-eight hours these areas assumed a hemorrhagic petichial appearance and were accompanied by intense itching. Within about twenty-one days the rash gradually faded and disappeared without any scarification.

On June 25, 1947, vigorous rubbing of small amounts of two types of electrode jelly used at the out-patient department, into small areas of each forearm, produced the same rash.

Scratch tests performed with the individual ingredients of the electrode jelly gave the following results:

Oil of pine needles—negative.	Gum tragacanth—2-plus.
Sodium benzoate—negative.	Glycerine—negative.
Sulfonated castor oil—negative.	Powdered pumice—negative.
Potassium bitartrate—negative.	Sodium chloride—negative.

A patch test with the gum tragacanth gave a positive reaction within twenty-four hours, and the resulting rash had the identical characteristics of the one obtained by the jelly.

Control tests on known allergic and nonallergic individuals with the same ingredients, did not elicit any positive skin reactions.

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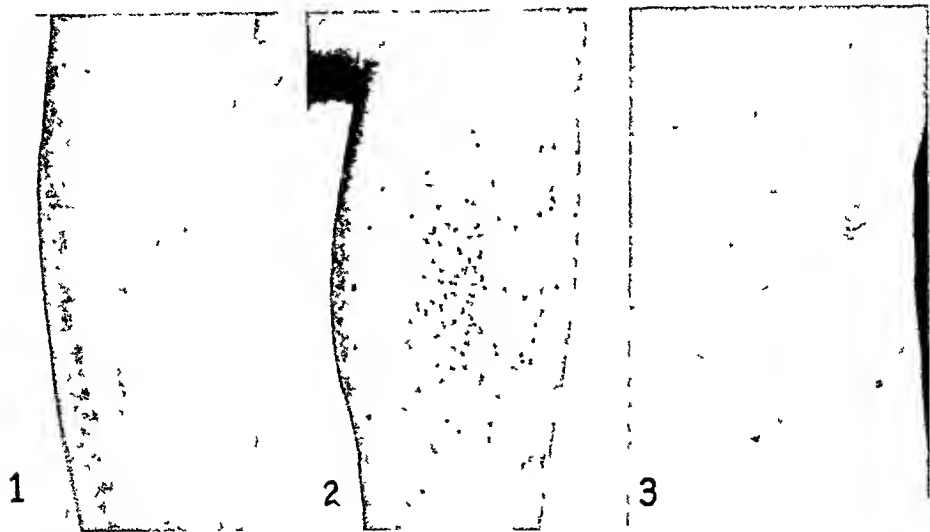


Fig 1. Erythematous patch on arm.

Fig 2. Hemorrhagic patch on leg

Fig 3. Erythematous patch on chest

#### COMMENT

The analysis of the history, namely, the typical appearance of a finely papular erythematous rash on two different occasions, localized at the sites of application of electrode jelly, strongly suggested hypersensitivity to one or more of the ingredients used in its manufacture. The result of the scratch tests shows unequivocally that the only ingredient incriminated was the gum tragacanth.

Although sensitivity to gum tragacanth has been known and described before,<sup>1,2</sup> I believe this is the first case of dermatitis caused by electrode jelly to be reported.

#### CONCLUSION

At present, all makes of electrode jelly contain gum tragacanth, and because of the rarity with which hypersensitivity to it occurs, it does not seem practical to advise any modification in its composition.

It may be advisable, however, to use a pad impregnated with saline solution, instead of the jelly, on such individuals.

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## PERSONAL EXPERIENCE WITH "ANTIHISTAMINICS"

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THE author has had mild "grass" hay fever for many years. Usually, this is controlled by a few preseasonal or coseasonal injections. This year, however, the pollen concentration was heavier than usual, and moderately severe hay fever was experienced. It was decided to use some of the newer antihistaminics. The following drugs and dosages were used:

Decapryn .....	25 mg.
Neohetramine .....	25 mg.
Pyribenzamine .....	25 mg.
Thenylene .....	50 mg.
Trimeton ..	25 mg.

*Results.*—All gave prompt and satisfactory relief. Within one-half hour after taking any of these drugs all symptoms of hay fever were gone. This relief lasted from six to eight hours. Usually, there were no more severe symptoms that day.

*Palatability.*—All of the drugs used had a bitter and unpleasant taste. The only exception was Thenylene, which is a coated tablet. It was not possible to swallow any of the tablets without getting some local taste. The following list is in order of decreasing palatability.

Thenylene  
Trimeton  
Pyribenzamine  
Decapryn  
Neohetramine

Both Neohetramine and Decapryn produced nausea and epigastric distress; Neohetramine was the worst. Pyribenzamine produced intestinal cramps and a mild diarrhea.

*Side Effects.*—All the drugs used produced drowsiness and diplopia. The feeling was not unlike that of overindulgence in alcohol. It was difficult to focus the eyes, there was a feeling of lassitude, and thought was slowed. Under these circumstances, it was very difficult to carry on a medical practice. These symptoms lasted for four or five hours and were succeeded by a mild headache. They could be made to recede more rapidly, but not to disappear, by taking dexedrine sulfate 5 mg. In general the side effects were fully as distressing and more incapacitating than the hay fever.

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When one compares the side effects of the antihistaminics with those of ephedrine, there is much to be said in favor of this almost neglected drug. The chief side effect of ephedrine is stimulation; this is not necessarily bad. Many hay-fever patients are already depressed and fatigued—yet they cannot stop work. To give them a drug which may depress them still further is not fair. What most of them want is relief so that they can still carry on. Ephedrine is certainly indicated here.

#### SUMMARY

It is not often (perhaps not often enough) that doctors must take their own medicine. It is realized that one case does not mean much—except to the individual concerned. However, in this case, since the patient is also the doctor, he has drawn certain conclusions, namely:

1. The newer antihistaminics are often unpalatable and they may produce distressing side effects.
2. Ephedrine is not unpalatable and its side effects are no more unpleasant than those of the other drugs.
3. Perhaps an ephedrine combination for daytime use and one of the antihistaminics for bedtime would be the most sensible procedure.

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#### NETHAPHYL IN BRONCHIAL ASTHMA

(Continued from Page 663)

2. Nethaphyl gave relief in asthma without side reactions of tachycardia, palpitation, rise in blood pressure and nervousness.
3. No toxic reactions were severe enough to cause cessation of treatment with the drug.
4. Nethaphyl is a valuable addition to the armamentarium of oral sympathomimetic drugs.

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## SOME UNCOMMON REACTIONS TO COMMON FOODS

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THE following case reports illustrate some uncommon reactions to common foods.

### CASE REPORTS

*Case 1.*—In August, 1935, a six-year-old boy who had recently developed asthma according to the history given by the mother was first seen at the Guthrie Clinic. From early infancy this boy had had eczema. Hay fever of a seasonal type became manifest at the age of three. The mother strongly suspected foods as the cause of the asthma, because buckwheat, spinach and egg white caused hives very promptly after ingestion. It was further added that during the preceding two weeks, wheat products, oranges and bananas had been eliminated with apparent relief. Carrot or foods containing carrot, on coming in contact with the oral mucus membrane, would provoke an immediate severe angioneurotic edema. What was not appreciated about this child's sensitivity was learned within the next hour when a nurse failed to note a request that carrot be omitted from the group of foods for which tests had been requested. Within a minute after the patient had received an intradermal test to a commercial extract of carrot in 1:10 dilution, he went into profound anaphylactic shock. During the next several minutes it appeared that a fatal reaction to a skin test might be encountered. The mother and maternal grandmother seemed unperturbed by the incident. Within an hour the reaction subsided by the usual methods of treatment, except for an intense generalized urticaria which persisted for six hours. When the relatives were commended for their calm behavior, the mother replied, "We have seen him this bad many times before from eating carrot."

*Case 2.*—In August, 1936, a sixteen-year-old girl with seasonal hay fever presented herself for study and treatment. During the taking of a detailed history, the patient told of the most annoying reaction to the odor of fish. It made no difference whether the fish was canned or fresh. The odor of fish cooking was also intolerable. The reaction consisted of marked coryzal symptoms with sneezing, which was followed by severe angioneurotic edema of the face and mild asthma. The patient could incriminate canned salmon and tuna and such fresh fish as cod, mackerel, shad and halibut. She had no knowledge of what shellfish might do. Skin testing by the intradermal method gave insignificant reactions to eighteen of the common fresh and salt-water fish, including the shellfish. This patient has been followed for the past eleven years, and she still reacts, but less violently, to the substances named above. She has since married and has two children, both of whom have had atopic eczema due to the citrus fruits and wheat.

*Case 3.*—In September, 1943, a twenty-eight-year-old married woman was referred because she had had four convulsions since 1940, characterized by an aura which was followed by loss of consciousness and tonic and clonic convulsions, but no loss of sphincter control. The aura consisted of a loud buzzing sound in the right ear of a few seconds' duration before loss of consciousness and convulsions manifested themselves.

There were frequent "spells" of a characteristic petit mal type experienced by

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this patient several times each week. The patient was referred to us for neurological study. It was during the course of history-taking that the patient mentioned her fondness for orange juice and that only recently she had some misgivings regarding its tolerance. There was no family history of allergy. Skin testing by the intradermal method gave a slight positive reaction to chocolate and orange. Both foods were withdrawn from her diet for several weeks, during which time there were neither petit nor grand mal seizures. When the patient tried orange juice, she suffered several petit mal attacks within a few hours after ingesting the juice of a single orange. Chocolate was found to be the cause of no trouble. She has avoided oranges for the past four years and has been entirely relieved of her attacks.

*Case 4.*—A forty-three-year-old man who had suffered from severe migraine since the age of sixteen, and who knew that lamb, chocolate, celery, pork and fish, except the shellfish, would cause the attacks, presented a history of petit mal since the age of thirty-five. On a few occasions these had been severe enough to be embarrassing. The attacks always occurred with the onset of a migraine headache. By elimination it was found that chocolate and celery were the offenders.

The family history was interesting. His paternal grandfather had migraine and intestinal manifestations (diarrhea) from egg regardless of how it was prepared. The father of the patient suffered occasional but severe attacks of migraine from unknown causes, though it was felt that nervous and physical fatigue were the contributing factors. About age forty-eight the father ceased having migraine and began to have attacks of unconsciousness of short duration, preceded by an aura described as a pressure sensation in the head. There were no convulsive movements.

The mother of the patient was extremely allergic to acetylsalicylic acid, suffering angioneurotic edema. A sister of the patient is similarly affected on taking this drug. Two children of the patient are allergic. A son has seasonal hay fever and eczema, due to chocolate and all the citrus fruits. A daughter has eczema due to wheat, egg, banana, corn, apple and the citrus fruits.

The patient stated that the odor of lamb cooking provoked an annoying sense of nervous tension and excitability. The eating of lamb was followed within twelve hours by severe migraine. English walnut will provoke a restless night accompanied by unpleasant dreams, all of which are associated with the feeling that he is chewing tobacco, and are accompanied by a sense of nausea and profound salivation. The patient's wife has to awaken him because of the marked restlessness displayed in these attacks. The pillow is generously saturated with saliva in these attacks.

Skin tests by both the scratch and intradermal methods to foods and inhalants are negative. By trial diet, chocolate and celery have been found to be the causes of the petit mal attacks.

*Case 5.*—A twenty-three-year-old woman sought advice regarding desensitization to chocolate. Total abstinence was recommended since she suffered from severe asthma following its ingestion. She remonstrated because she loved the taste of chocolate, and its odor provoked a craving that was difficult to satisfy. To this she added an interesting comment which was readily confirmed by obtaining her old hospital records. She was born in 1915 in the obstetrical section of the Packer Hospital. During the first few days of life she presented a terrifying picture of severe respiratory difficulty which was reluctantly termed asthma. Her problem aroused considerable interest, and one of the many consultants who saw her thought that the mother's breast milk might be the cause and advised formula feedings. The response was favorable and dramatic, but the real answer to the problem was not forthcoming for some years. Not until the child became old enough to be given candy, and her marked sensitivity to chocolate was discovered, was the story com-

## UNCOMMON REACTIONS TO COMMON FOODS—LANGLEY

pleted. It was revealed that the mother was so strongly desirous of nursing this child that to insure a good supply of breast milk she indulged heavily in chocolate both prepartum and postpartum. Unquestionably, the mother's breast milk contained sufficient allergen to excite the response noted.

In order to accommodate this young lady, oral desensitization to chocolate, according to the suggestion of Kesten,<sup>5</sup> was tried. The result was not satisfactory, because even insignificant amounts of chocolate still provoked asthma within fifteen to thirty minutes, lasting for a day or more and requiring epinephrine at intervals for comfort.

### DISCUSSION

A search of the literature will reward one with reports of unusual reactions or expressions of sensitivity to foods. Feinberg,<sup>2</sup> Rowe<sup>6</sup> Urbach<sup>8</sup> have covered these references in their textbooks. The first case presented in this paper represents a most intense reaction to a common food. It has been learned that the patient has improved encouragingly over the years although carrot still provokes an intense reaction, as does buckwheat, but other foods are tolerated without reaction.

The problem of epilepsy has intrigued many investigators. The above authors have considered the numerous available publications dealing with the probable allergic basis of this disease. In this writer's experience the two cases here reported are the only definite proven instances in a small but substantial series investigated. Two other cases of epilepsy might be added to this report, but they have not been followed for a sufficient length of time to justify their inclusion. It is not felt that idiopathic epilepsy is of allergic origin, but rather that epileptiform seizures can occur in individuals who are allergic and that food allergy is a contributory factor.

The case of sensitivity to chocolate occurring in the mother's breast milk may not warrant too much discussion because breast feeding seems to be unpopular. Shannon<sup>7</sup> and also Donnally<sup>1</sup> have shown, however, that food proteins can be excreted in breast milk in sufficient amounts to cause reaction in the nursing child. It is not surprising, therefore, that this patient should have had, in the first days of life, such intense reaction.

Finally, proof is not wanting of the fact that food odors, especially from food cooking, produce sufficient allergen in the air to cause reactions in susceptible individuals. Feinberg,<sup>2</sup> Hoersht,<sup>4</sup> and also Urbach<sup>8</sup> have presented their experiences and observations in this group of patients.

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# THE SIGNIFICANT ALLERGENIC AIR-BORNE NONPATHOGENIC BACTERIA, THEIR INCIDENCE, TYPES OF ALLERGIES AND TREATMENT

## A Three-Year Study

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IN the autumn of 1944, while summarizing the beneficial effects of the treatment of intrinsic allergies with an antibiotic,<sup>1</sup> we noticed that several of our patients, with definitely intrinsic allergies, who were cleared with antibiotic treatment, showed a recurrence of symptoms with the start of the autumn season. Their trouble was definitely of atmospheric origin, but as usual at this time of the year there were no pollens and only a few fungus spores found on our daily exposed slides. We then exposed petri dishes containing dextrose-agar daily to the open air. These exposures were made for five minutes on the seventh floor of an office building in the center of town. The exposed petri dishes were placed in the incubator and bacterial colonies developed in great numbers. This investigation began on October 10, 1944, and was continued until May 17, 1945. The organisms found on the test plates were always about the same, independent of atmospheric conditions, and also independent of the location, whether in town or in the suburbs. Regardless of the elevation above the ground, of the temperature of the outside air and the humidity, the colonies examined and identified by Dr. Borg of the Department of Microbiology of the University of Washington consisted of a great array of organisms characteristic for air-borne bacteria. Some were Gram-positive, like *micrococcus tetragenus*, *micrococcus luteus*, or *Bacillus petasites*; and some were Gram-negative like *Pseudomonas aeruginosa*, or spore-bearing bacteria like *Bacillus megatherium*, *Bacillus mycoides*, and *Bacillus subtilis*. Prominent in this group was *Aerobacter aerogenes*.

All these bacteria are nonpathogenic under normal conditions, but they are definitely allergenic and often cause allergic symptoms when the usual atmospheric allergens, such as pollens, mold spores, and various dusts, are not in the picture at all. Recognition of these not uncommon causes of allergic disorders is necessary in order to diagnose and treat some of the allergic diseases with which we have to deal.

In 1942 the American Association for the Advancement of Science published a volume entitled "Aerobiology" containing a number of articles about air-borne bacteria. In one of the articles Dr. E. C. Stakman says, "Relatively little is known about air-borne bacteria as possible allergens. The number of bacteria in the soil, their ability to survive in dry soil and their dissemination with dust suggest their possible effect on human beings and should be investigated."

Our investigation shows that a number of patients with intrinsic

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allergies caused chiefly by an allergy to air-borne (nonpathogenic) bacteria. Some of these patients will also react to pollens, mold spores and respiratory bacteria, but the important cause of their allergic troubles are nonpathogenic air-borne bacteria which are very common and widely distributed.

The progress in the diagnosis and treatment of allergies is made by gradual elimination of all the hitherto unknown causes of allergic disorders and their successful treatment. Of the many atmospheric causes of allergy, air-borne bacteria have been overlooked but should be investigated in every case where pollen, mold, and dusts have been found and treated and where there still remains a seemingly mysterious air-borne cause of allergies.

During this investigation between October, 1944, and the end of 1946, 423 colonies were studied and identified. A summary of the findings shows that they contained amongst others *Bacillus mesentericus*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis* and *Micrococcus luteus*. Others were identified as *Micrococcus conglomeratus*, *Micrococcus candidus*, *Micrococcus epidermidis* and *Micrococcus flavescens*. Further identifications revealed the presence of *Micrococcus flavus*, *Micrococcus roseus*, *Bacillus cereus*, *Bacillus mesentericus*, *Bacillus petasites*, *Bacillus mycoides*, *Bacillus polymyxa* variety *acetoaethylicum*, *Bacillus atterimus*, *Bacillus megatherium*, and *Bacillus vulgatus*. All these bacteria are nonpathogenic under normal conditions, but they are definitely allergenic and often cause allergic symptoms when the usual atmospheric allergens, such as pollens, mold spores and various dusts, are not in the atmosphere.

TABLE I. SUMMARY  
Total Number of Cases—155

Results of Treatment:		
Asymptomatic .....	29	131 Positive Results or 84.4%
Marked Improvement .....	57	
Moderate Improvement .....	45	
<hr/>		
Slight Improvement .....	9	
No Improvement .....	11	
Moderately Worse .....	1	
Variable .....	2	
Condition Not Known .....	1	
<hr/>		
		155

Types of Allergies	
Rhinitis (Hay Fever) .....	60
Asthma .....	112
Urticaria .....	8
Dermatoses .....	23
Migraine .....	14
Gastrointestinal .....	3
Mixed .....	62

## CASE HISTORIES

Skin testing was done with a dilution of 1:1,000 of the stock vaccine. This dilution therefore contained four million organisms to the cubic centimeter. The skin reactions were usually very definite.

*Case 1.*—A married woman, fifty-two years of age, developed a severe cold in May, 1943. A persistent cough remained, and asthma was diagnosed by a physician in July, 1943. A definite respiratory wheeze was noticed after January, 1944. On the basis of skin tests a diagnosis of tuberculosis was made. The chest x-ray was nega-

tive. A positive sputum was reported in February, 1944. Treatment consisted of bed rest, epinephrine inhalations and various cough remedies. There was no improvement.

In March, 1944, the patient complained of a severe cough, purulent sputum, moderate dyspnea and wheezing. There was a mild atopic dermatitis on the lower extremities. Her clinical history revealed exacerbations of her symptoms on the seashore, out of doors, during the cool damp months, and on exertion. Physical examination revealed a typical moderately severe bronchial asthma and a dry, red, scaly, sharply demarcated macular rash on the lower extremities. Chest x-ray, blood count, and sedimentation rate were normal; PPD, 3-plus. Sputum: no acid-fast bacilli were found.

Family history was negative for allergies.

Skin tests: Intradermal tests for molds and the local pollens were positive. Intradermal tests were made for a mixture of Gram-positive and Gram-negative air-borne bacteria.

Treatment: Treatment with the reacting allergens, namely, mold and pollen extracts, and air-borne vaccines was started on April 13, 1944. Tests for *aerobacter aerogenes* were done on May 10, 1944, and gave a 2-plus reaction.

In June, 1944, she began to improve and showed marked improvement after February 7, 1945. When last seen on November 4, 1946, she had only a slight cough and no asthma. The skin was clear, and she showed a marked gain in weight.

*Case 2.*—A woman, aged thirty-four, reported at this office February 2, 1944, complaining of recurring hives between January and August, and a mild cough. The symptoms started two weeks after moving to Seattle from Utah, four years previously. She thought that her symptoms seemed to be worse after eating pork, green beans, wheat, pineapple, chocolate, and walnuts. There was a definite aggravation during the spring and summer, from house dust and while riding out of doors.

A sister had hives.

Previous treatment consisted of injections taken three years previously after a series of skin tests. There was no improvement.

Physical and laboratory examinations were negative.

Skin tests were positive to summer and fall pollens, dust, respiratory bacteria, and a few foods.

Treatment consisted of hyposensitization to the inhalants and an elimination diet. Improvement was irregular and temporary.

Intradermal tests for air-borne bacteria were made on October 23, 1944, and treatment started immediately. There was noticeable improvement after April 4, 1945, with fewer and milder relapses. When seen on March 5, 1946, she had no respiratory symptoms and only occasionally a few hives.

*Case 3.*—A woman, twenty-nine years of age, gave a history of hay fever and asthma of eight months' duration. She had previously suffered from asthma from the ages of eighteen months to eight years. There are multiple family allergies.

Physical examination showed a well-nourished woman with the typical findings of allergic rhinitis and bronchial asthma. There was a nonpathological mitral systolic murmur.

The allergic study showed her to be sensitive to various pollens of trees, ferns, molds and respiratory bacteria. She was given hyposensitization treatment and was relieved until September, 1944, when she had a recurrence of her symptoms. She was tested intradermally with a 1:100 dilution of air-borne bacteria. She reacted moderately to Gram-positive bacteria. Proper vaccine was added to her treatment on October 25, 1944. Improvement was noticed immediately, and on March 3, 1947, she was discharged as asymptomatic.

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*Case 4.*—A man, aged thirty-four years, an aeronautical engineer, stated on March 16, 1944, that he had had a substernal wheezing and a postnasal drip for three years following an attack of influenza. Exacerbations seemingly were not seasonal but were more frequent in damp, windy weather.

Previous injections containing a vaccine and house dust had given moderate temporary improvement. A subsequent series of injections produced no benefit.

There were no known allergies among his blood relations.

His past history was essentially negative.

Physical and laboratory examinations suggested no active pathologic condition.

Skin tests showed him to be allergic to dust, and coniferous tree pollen, and to a lesser extent, the spring and summer pollens.

He was tested for air-borne bacteria on October 27, 1944, and reacted positively to Gram-positive and to Gram-negative mixtures. Treatment with vaccines of both types of bacteria were started immediately, and improvement was noticed in January, 1945.

Temporary relief was obtained from hyposensitization treatment to the positive reacting allergens.

A subsequent left supraclavicular adenitis, edema and ptosis of the left eye, weight loss of 20 pounds, various gastrointestinal disturbances, and nervousness developed. He then remarked that he had had a mole removed. A diagnosis of metastatic sarcoma was made.

The patient moved to the Middle West, and the outcome of the case is not known.

*Case 5.*—On September 13, 1944, a woman, aged forty-eight years, complained of a chronic rhinitis of progressing severity of seven years' duration. It was nonseasonal. She noticed that the symptoms were much worse when she was exposed to house dust and temperature changes, and when constipated. There was occasional itching of the ears, nose and palate, and moderate aching in the right occipital area.

There was a past history of arthritis, angioneurotic edema in 1941, cholecystectomy 1938, and two tonsillectomies.

Family history for allergies was negative.

Previous treatment consisted of epinephrine injections and benzedrine inhalations which gave only slight relief. There had been no previous allergy study.

Physical examination was essentially negative except for an allergic-appearing nasal and pharyngeal mucus membrane.

Skin tests were positive for respiratory bacteria, late summer pollen, house dust, and a few foods.

Treatment consisted of an elimination diet, hyposensitization, and various symptomatic measures. There was no tangible improvement.

She was tested for air-borne bacteria on November 6, 8, and 15, 1944. Treatment began immediately with a Gram-negative mixture, and since then there has been a gradual, moderate improvement in her chief complaint, i.e., the rhinitis, although there have been episodes of various cerebral, gastrointestinal, and joint symptoms. She states that generally her condition is much better, and we feel that the prognosis is good.

*Case 6.*—A girl, age six, complained on January 14, 1944, of a chronic, perennial rhinitis since infancy. Exacerbations occurred during the summer and when indoors. There were no food dislikes and no history of food disagreements.

Many of her blood relatives present allergic complaints.

Physical examination was essentially negative.

Intradermal allergen tests were positive to spring, summer and fall pollens, and a dust mixture. On November 2, 1944, she was tested for air-borne bacteria and reacted strongly, more so to the Gram-positive mixture. Treatment was started, and

improvement began immediately. By May, 1945, the child was fine. She was free of symptoms, and treatments were stopped in September, 1945.

*Case 7.*—A woman, forty-two years of age, came to the office June 7, 1944, complaining of progressively severe asthma following a cold in January, 1943. She had had frequent colds for the preceding three years. The eating of peas had always produced nausea. The symptoms were aggravated when at home.

The past history revealed ringworm at age nine, and the removal of nasal polyps in 1934. She had spent her entire life on the West Coast.

There was no family history of allergy.

Physical examination elicited a slight roughening of the breath sounds, and a typically allergic-appearing nose and throat with small polyps in the right posterior nasal cavity.

The skin reacted violently to tests of summer and fall pollens, dust, fungi, dog hair, house dust, and respiratory bacteria. Local and general reactions occurred after the tests, requiring the administration of aminophyllin by vein. She was tested for air-borne bacteria on November 3, 1944, and reacted strongly to the Gram-positive mixture. On November 25, 1944, she was tested for another Gram-positive mixture, to which she reacted positively (2-plus).

Hyposensitization treatment produced a gradual and variable improvement. On one occasion an Arthus phenomenon from a dust injection occurred after the patient had unwittingly exposed herself to a massive dose of dust. The subsequent dilution of the dust extract had to be reduced from 1:1,000 to 1:500,000.

The air-borne vaccine was started November 3, 1944. Improvement was experienced about three weeks later. When last seen on January 20, 1947, she was symptom-free.

*Case 8.*—A man, aged sixty-two, with no family history of allergies, complained on March 20, 1944, of a severe morning cough accompanied by a marked dyspnea. The duration had been three years. Athletes foot had been present for many years, and he had had gout in the left great toe for one year. No specific previous treatment had been given.

Physical examination revealed a moderate postnasal drip, edema and hyperemia of the nasal and pharyngeal mucus membranes, a slight deviation of the nasal septum to the left, and an epidermophytosis on the left foot. Fluoroscopic examination of the chest showed a slight increased density in both apices, and a moderate myocardial hypertrophy.

The skin reacted to tests of tree and weed pollen, house dust and trichophyton. He was tested for air-borne bacteria on December 26, 1944, and gave mild reactions to Gram-positive and Gram-negative bacteria and to aerobacter. Treatment was started immediately, and improvement was noticeable.

Thereafter, improvement in symptoms was evident and on June 26, 1945, he was discharged as asymptomatic.

*Case 9.*—A man, fifty-eight years of age, reported April 3, 1944, complaining of asthma for one year, with the onset after he moved to the coast from Idaho. He had had a cough for four or five years. The initial trouble started after an attack of influenza. No known allergies existed among his blood relations. Past history was irrelevant.

Physical findings were not important.

All skin tests were negative except to the respiratory bacteria and fungi. Later tests showed him also sensitive to air-borne bacteria.

Hyposensitization treatment produced a marked but variable improvement.

The addition of the air-borne bacteria-vaccine to the treatment improved the situation, but the case terminated in only slight improvement. The treatment definitely



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was not given a fair chance. It is well known that time is required to establish adequate immunity to practically all of the allergenic bacteria, and that necessary time was not at our disposal.

*Case 10.*—A housewife, aged thirty, came to the office June 5, 1945, complaining of asthma and hay fever of five years' duration.

She had had chronic recurrent colds since childhood. The symptoms were perennial, intermittent, worse in late spring and summer and after the menses. House dust seemed to aggravate her troubles.

Her past history revealed eczema and hives and frequent colds in childhood.

Multiple allergies are present in the maternal side of her family.

No improvement was experienced from a previous elimination diet following skin tests.

Physical examination revealed an occasional faint, evanescent wheeze. The heart, blood count, sedimentation rate, and Wassermann test were negative.

Skin tests were positive to coniferous tree pollen and various dusts.

Variable improvement was noticed after an elimination diet and injections consisting of the positively reacting inhalants.

The nonpathogenic air-borne bacteria vaccine was started September 11, 1945, three months after beginning of treatment. Some consistent improvement was beginning to be noticed five months later, February 27, 1946.

Excepting an intervening pregnancy which caused some aggravation, the patient is free of symptoms.

### COMMENTS

Skin tests and the positive results of treatment with a vaccine made from air-borne bacteria demonstrate that an allergy to these bacteria exists in many cases. While assays against cultures of air-borne bacteria showed that they were affected moderately by penicillin and more strongly by streptomycin, we have found that treatment with a vaccine prepared from air-borne bacteria was a reliable, if slow, remedy in such conditions. The vaccines have to be very weak, as apparently these bacterial extracts are very active and strong. Our stock vaccines contained four billion organisms per cubic centimeter, which is the strength of most commercial bacterial vaccines. Treatment was started with dilutions of 1:1,000 of the stock vaccine. The dosage was slowly increased, and invariably good desensitization resulted. After some experience we found that we needed only three stock vaccines for treatment of all these cases of allergy to air-borne bacteria, namely, one made from Gram-positive, one made from Gram-negative air-borne bacterial cultures, and one from the *Aerobacter* group cultures. Skin testing was done with the same vaccines, diluted 100 or 1,000 times.

When an allergy to air-borne bacteria exists, the routine treatment for the usual allergens falls short of complete relief. Therefore, allergies to air-borne bacteria must be considered an important cause of symptoms and should be an intrinsic part of the diagnosis and treatment.

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# ALLERGIC ECZEMATOUS CONTACT-TYPE DERMATITIS FROM ODD THINGS OR IN ODD WAYS

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THE following case reports illustrate situations in which well-known eczematogenous allergens caused dermatitides in unusual places or by uncommon mechanisms. In one case an unlikely contactant caused an eruption on skin sites on which more obvious substances seemed implicated.

*Case 1.*—Allergic eczematous contact-type dermatitis of the buttocks from the wood of a plastic-paint-covered and undamaged toilet seat.

C. M., a boy, aged twelve, presented an eczematous eruption on the lower quadrants of the buttocks and the upper portions of the thighs. The localization of the rash very plainly implicated a toilet seat. The eruption was more extensive on one side than the other due to the fact that the patient characteristically sat in such a position as to cause greater contact and exposure on the more affected side. Patch tests with slivers from the painted side of the toilet seat were negative, but strongly positive reactions (4-plus) was elicited by the unpainted wooden side. This unexpected finding was confirmed by repeated tests. The species of wood was not botanically identified.

*Case 2.*—Allergic eczematous contact-type dermatitis of the fingers, neck and lips from the dyes of nylon threads.

A. G., a seamstress, specialized in sewing button holes with nylon thread. An eczematous eruption appeared on the fingers, lips and across the neck in the fashion of a necklace. The patient herself suspected the nylon thread as the cause of her dermatosis and proved the point prior to medical investigation by tying a piece of the material around her wrist. Within two days a vesicular dermatitis in the shape of a bracelet promptly occurred. The lesions on the fingers corresponded to the way in which the nylon threads were manipulated in the sewing process; the eruption on the neck corresponded to the places where lengths of thread were held for successive use; the cheilitis was caused by wetting of the threads with the lips to facilitate threading of the needles.

This case, among others, was extensively studied by Dobkevitch and Baer.<sup>1,2</sup> These workers showed that in their cases the allergen involved in nylon-stocking dermatitis was the dye. They explained further that the sensitizing dyes which had been used in nylon stockings were converted on the skin into compounds which are chemically and immunologically related to paraphenylenediamine in its conversions.

Table I is an abridged protocol of the patch tests performed on this patient.

*Case 3.*—Allergic eczematous contact-type dermatitis of the face and other parts of the body from contamination of innocent cosmetics with nail polish or other strong sensitizing agents.

B. W., a housewife, presented an eruption on the brow, cheeks, neck and hands. Clinical experience suggested a cosmetic applied widely to the body. Patch tests were performed as shown in Table II.

This case is representative of a group of patients who are very sensitive to nail

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# CONTACT-TYPE DERMATITIS—LEIDER AND FURMAN

TABLE I

Test Substance	Reading	Remarks	Dates
Waxed nylon thread, navy Waxed nylon thread, brown Waxed nylon thread, black Wax, as is Paraffin, as is (2% in pet.) Unwaxed nylon thread, gray Unwaxed nylon thread, tan Control gray silk thread Nickel sulphate, 5% aq. sol. Rubber glove, stock specimen	1 plus 2-3 plus 2-3 plus Negative 2-3 plus 1-2 plus 1-2 plus Negative Negative 1-2 plus	Note positive reactions to paraphenyldiamine and to rubber glove in addition to the positive reactions to the various nylon threads.	Tested 11/9/47 Read 11/11/47
Brand A nylon hose Brand B nylon hose Brand C nylon hose Brand D nylon hose Patient's nylon hose Patient's rubber glove	3-4 plus 3-4 plus 3 plus 1 plus 2 plus 3 plus	Note positive reactions to all brands of nylon hose including patient's, and to her rubber glove.	Tested 11/29/47 Read 12/1/47
Brand E dyes I-IV, as is Brand E dyes V & VI, as is Nylon thread, undyed Brand C dyes I & II, as is Brand B dyes I & II, as is	Negative 2-3 plus Negative 3-4 plus 3-4 plus	Note positive reactions to several dyes and absence of reaction to undyed nylon thread.	Tested 12/20/47 Read 12/22/47

TABLE II

Test Substance	Reading	Remarks	Dates
Cleansing cream Orange skin cream Skin lotion Nail polish	3 plus Negative Negative 2 plus	Note strong reactions to cleansing cream and to nail polish.	Tested 3/26/47 Read 3/28/47
Cleansing cream (material taken from bottom of jar) Nail polish	Negative 2 plus	Note absence of reaction to uncontaminated portion of cleansing cream.	Tested 4/2/47 Read 4/4/47
Skin lotion Orange skin cream (material taken from top of jar) Nail polish Mum (deodorant) Cold cream (material taken from bottom of jar) Cold cream (material taken from top of jar)	Negative 1 plus 3 plus Negative Negative 2 plus	Note confirmation of previous test findings and proof of contamination of other preparations with nail polish.	Tested 4/7/47 Read 4/9/47

polish and who, at first, give the impression of being sensitive to other cosmetics which are not related to nail polish. Such coincidence would not be remarkable if the reactions were due to concomitant sensitivity to nail polish and, say, hair lacquer, but concomitant sensitivity to nail polish and several creams must be statistically rare. Upon analysis it has been repeatedly discovered that polish from the finger nails easily contaminates other cosmetics concurrently applied.

In Tables III and IV, and in the following paragraph, are presented additional miscellaneous cases which reveal, by critical patch testing with selected portions of the implicated substances, allergenic contamination of innocent cosmetics by notorious sensitizing agents.

D. B., a worker in leather belts and handbags with an eruption of the hands, antecubital fossae and axillae, was discovered upon routine testing to be very strongly reactive to paraphenyldiamine and moderately so to the commercial deodorant she was currently using. Critical patch testing, however, showed the same strong re-

# CONTACT-TYPE DERMATITIS—LEIDER AND FURMAN

## TABLE III. CASE OF C. S.

Test Substance	Reading	Remarks	Dates
Nail polish Cold cream Paraphenyldiamine (2% in pet.) Lipstick Face powder Pyrethrum, as is DDT (5% in acetone)	3 plus Plus-minus Negative Negative Negative Negative Negative	Note strong reaction to nail polish and suggestive reaction to cold cream.	Tested 6/2/47  Read 6/4/47
Cold cream (material taken from top of jar) Cold cream (material taken from bottom of jar) Nail polish	2 plus  Plus-minus  3 plus	Note proof of contamination of cold cream by unequal reactions corresponding to degree of contamination.	Tested 6/4/47  Read 6/6/47

## TABLE IV. CASE OF M. M.

Test Substance	Reading	Remarks	Dates
Bath powder Mascara cream Rouge Sub-tint cream Wave lotion Perfume Face powder Lipstick	Negative Negative Negative 2 plus Negative Negative Negative Negative	Note apparent implication of sub-tint cream alone. Test with nail polish not yet done.	Tested 4/23/47  Read 4/25/47
Nail polish Sub-tint cream (old jar) Sub-tint cream (new jar)	2 plus 2 plus Negative	Note proof of contamination of sub-tint cream by nail polish.	Tested 4/25/47  Read 4/27/47

actions to paraphenyldiamine, to samples of her tan, brown, blue, black garments, and to occupational materials, but a negative reaction to a newly purchased specimen of the same deodorant. In this instance the old jar of deodorant must have been contaminated by traces of the dye clinging to the fingers from domestic or occupational manipulations.

*Case 4.*—Allergic eczematous contact-type dermatitis of the female breasts from sponge rubber prostheses ("falsies," "gay deceivers").

T. G., a stenographer, acquired and wore a pair of sponge rubber mammary prostheses. About two weeks after use of these devices, an erythematous, scaly eruption appeared on the outer, lower quadrants of the true mammae. Patch tests with pieces of the sponge rubber on unaffected sites of the breasts reproduced the eruption in these areas.

### COMMENT

The first case, describing the sensitivity to wood of a toilet seat heavily covered with paint, illustrates a phenomenon incredible to the inexperienced, namely, the ability of an allergen to pass through seemingly impervious barriers and successfully challenge the skin. However, the positive patch tests, and the clinical tests of improvement upon avoidance and exacerbation upon re-exposure, prove the causal relationship. Such instances lead to the inescapable conclusion that some allergens have remarkable capacities to elicit reactions with amounts that would appear to be chemically undetectable.

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The second case report illustrates, among other things, the well-known importance of occupational operations in localizing the sites of contact-type dermatitis. More important, it further demonstrates that, for some substances, minor additions or unavoidable traces of agents that are of small compositional importance in the parent mass (azo-dyes in the case in point) may be responsible. Similar examples are to be found in the minute amounts of formalin in plastics and in soap which provoke and evoke allergic sensitivity, whereas the actual plastic or other soap ingredients may be inert. Most important of all, it reveals strikingly the phenomenon of cross-sensitization between allergens. This fact, as had been fully discussed and stressed by Sulzberger,<sup>3</sup> explains the persistence and chronicity of some allergic dermatoses in spite of apparent avoidance of causal substance. Appreciation of the situation will sharpen search for immunologically related agents and will inevitably lead to discovery and cure in a greater percentage of cases.

The third report illustrates the very common circumstance in which tests can be misleading if their interpretation is hasty or uncritical. A knowledge of the intimate habits of persons of both sexes and of all types and stations is shown to be of value. If one were to devise a means of tracing the transport of substances by the hands to other parts of the body, the locations on which deposit is made would surprise the unimaginative. Far-flung distribution of substances by handling, and the multiplicity of common substances that are of eczematogenic potential, are two very significant considerations in discovering causative agents and in solving obscure problems. In the cases cited, the contamination of innocent preparations by minute amounts of powerful sensitizers may either incriminate harmless agents without implicating the actual offenders, or, if the contaminating event is not realized, may perpetuate an eruption despite removal of the apparently offending substance.

The fourth report is representative of similar, more banal events like eruptions from hearing aids, telephones, and artificial limbs.

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# A CLINICAL EVALUATION OF A NEW ANTIHISTAMINIC DRUG. "ANTISTINE"

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WITH the advent of the new antihistamine drugs, the field of palliative therapeutics in allergy has been greatly enhanced. In the last year or so there have been numerous reports on the use of Benadryl and Pyribenzamine. Here we have attempted to give a clinical analysis of the efficiency of one of the newer antihistaminics, namely, Antistine.\*

Antistine is Ciba's trade name for an antihistaminic preparation, whose chemical formula is phenyl-benzylamino methyl-imidazoline. For oral medication, the hydrochloride salt is used, while topically in the eye and nose the sulfate is preferred. Animal experiments<sup>3</sup> would seem to indicate that this drug is from two to ten times less toxic than Pyribenzamine, depending on the route of administration. From evidence presented by animal experimentation<sup>3</sup> it would seem that Antistine has definite antihistamine activity.

Several European reports have been published on the use of this drug. Schindler<sup>7</sup> investigated its effect on thirty-nine allergic patients. Of this number, ten had bronchial asthma, eleven had urticaria, fifteen had pruritic conditions. He used the oral, subcutaneous and intravenous routes of administration. His average daily dose was 300 mg. orally; however, twice this amount was tolerated. Parenterally, the dose varied up to 300 mg. No unpleasant secondary effects were observed. He found that the therapeutic effect in urticaria was very good; in pruritus and in some cases of asthma, it was good. In two cases of erythema nodosum it was ineffectual; however, the articular pains in a case of scarlet fever rheumatoid disappeared on the second day of treatment.

Brack<sup>2</sup> found that Antistine, in addition to its inhibiting effect on itching produced by histamine, had a slight local anesthetic effect. He found that, in proper dosage, it will reduce or counteract the itching in urticaria, eczema, neurodermatitis, prurigo, lichen ruber planus, psoriasis, and nervous pruritus without skin changes and in scabies. To completely suppress the itching, doses which caused temporary mild dizziness were occasionally employed. In urticaria, not only the itching but the skin changes were prevented. Direct influence on the skin changes in other dermatologic conditions was not observed. The only undesirable secondary effect observed was occasional mild dizziness.

Bourquin<sup>1</sup> used Antistine eye drops in numerous eye conditions, and recommends it especially in allergic eye conditions. He found that photophobia, itching and lacrimation were favorably affected. Meier and

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\*Antistine was supplied through the courtesy of the Ciba Pharmaceutical Company, Summit, N. J.

Bucher<sup>5</sup> in animal experiments found that Antistine has definite antagonism to histamine when applied locally or generally. They<sup>6</sup> further demonstrated that this drug does not inhibit the antibody production stimulated by repeated antigen injections; in fact, animals given Antistine had a considerably higher titre, and they postulate that this might have been due to the fact that these animals were able to tolerate a much larger amount of antigen which might possibly have been the basis for the increased antibody production.

Friedlaender and Friedlaender<sup>4</sup> found that Antistine afforded guinea pigs protection against histamine shock. They further found that in 50 to 100 mg. doses it gave symptomatic relief in the majority of cases of allergic rhinitis and urticaria. Less benefit was apparent in asthma, atopic dermatitis, contact eczema and allergic headache. They felt that Pyribenzamine was more effective when used in the same patient, although a small percentage found Antistine superior. Antistine eye drops produced symptomatic relief of burning and itching in cases of allergic conjunctivitis. The side effects from Antistine were generally less frequent than with Pyribenzamine, and in a group of patients in whom the two drugs were compared, it was found that frequently those unable to tolerate Pyribenzamine were able to tolerate Antistine in effective dosage.

In our series of cases, there was no attempt made at selection of patients. The drug was given for the presenting symptoms in cases of asthma, hay fever, atopic eczema, contact type eczema, allergic conjunctivitis, and gastrointestinal allergy. Many of these patients were undergoing hyposensitization therapy, and for one reason or another, were symptomatic. Of these patients, many were just starting therapy for the first time, while others who had been under treatment for ragweed hay fever for a number of years, developed either tree or grass hay fever for the first time this year, necessitating some palliative therapy.

Of the patients taking the drug the duration varied from one week to 133 days. The dosage employed by these patients was a 100 mg. tablet three to four times daily. Many of the patients had never been on any previous antihistamine therapy while the others had been on Benadryl or Pyribenzamine and, because of the severity or persistence of side effects, had had to discontinue them. One patient was hospitalized on two occasions last year, due to severity of side effects from Benadryl and Pyribenzamine. He was able to tolerate 300 to 400 milligrams of Antistine with the only side effect being slight nausea.

Table I shows the clinical results obtained with the use of Antistine. The various categories into which these patients fitted are shown; in addition, the patients are divided into adults and children. Although the results with asthmatic symptoms were disappointing, the cough was controlled in most cases. In the four cases of conjunctivitis, only local therapy consisting of 0.5 per cent Antistine eye drops was used.

We found the drug to be very efficacious in children because adequate

# "ANTISTINE"—KAPLAN AND EHRLICH

TABLE I. CLINICAL RESULTS WITH ANTISTINE

Allergic Manifestation	Adult	Children	Fair		Good		Excellent		Poor	
			No.	%	No.	%	No.	%	No.	%
Hay Fever	21	15	6	15	20	51	10	26	3	8
Perennial Allergic Rhinitis	12	7	6	32	5	29	3	16	5	26
Asthma and Hay Fever	14	10	3	12	14	58	2	8	5	21
Chronic Urticaria	4	0	0	0	1	25	0	0	3	75
Atopic Eczema	3	1	0	0	1	25	1	25	2	50
Contact Eczema	3	0	0	0	2	66	0	0	1	33
Conjunctivitis	3	1	0	0	2	50	2	50	0	0
Gastro-Intestinal Allergy	1	1	0	0	0	0	1	50	1	50

These cases were evaluated both subjectively and objectively within the limits of such an evaluation, which, it must be admitted, is frequently not good. Subjectively we depended on the patient's statement as to how he felt. Objectively we examined the patient. Those cataloged as poor had no relief whatsoever. Those classified as fair had equivocal results; those reported as good had approximately 50 per cent relief, and those who were listed as excellent had either complete or practically complete relief.

TABLE II. SIDE EFFECTS\* OBSERVED WITH  
ANTISTINE

Nausea .....	6
Sneezing (?) .....	1
Dryness of mouth .....	4
Dizziness .....	2

\*In one case the severity necessitated discontinuance of the drug.

TABLE III. COMPARATIVE SIDE EFFECTS IN PATIENTS WHO HAD TAKEN  
PYRIBENZAMINE AND/OR BENADRYL AND/OR ANTISTINE.

	Number of Patients	Number having Side effects	Per Cent
Antistine .....	99	13	13†
Pyribenzamine .....	21	10	47*
Benadryl .....	18	16	88*

\*Of these, five patients had to discontinue because of severity of side effects.

\*\*Of these, sixteen patients had to discontinue because of severity of side effects.

†One couldn't take Antistine.

dosage could be given while side effects were minimal. It is interesting to note that of the few side effects that our patients experienced, none occurred in children.

From our experience, we feel that the 100 mg. Antistine tablet has roughly the therapeutic effect of the 50 mg. Pyribenzamine tablet with, however, less side effects. When this study was first undertaken, the tablets were in 50 mg. size, and with this amount, no side effects were observed, but therapeutic results were also quite negligible. We then tried 100 mg. on a number of patients, and palliative effectiveness increased. Subsequently, after discussion with Dr. Mayer of Ciba, the tablets supplied to us were 100 mg. size.

In Table II we have tabulated the few side reactions which our patients experienced. In one of these, the symptoms were severe enough to necessitate discontinuance of the drug. This patient, strangely enough, experienced severe sneezing spells each time she took a tablet; this occurred on three successive days. She had a perennial allergic rhinitis, and at the time of medication her complaint was a stuffy nose, but she had no sneezing spells.

Table III shows the comparative effects in some patients who had taken either Pyribenzamine and Antistine, Benadryl and Antistine, or had taken



all three. The figures on Pyribenzamine and Benadryl are obviously misleading for several reasons: firstly, the number of patients on whom the comparison was made, was quite small. Secondly, and more important, these represent only those patients who had taken Pyribenzamine or Benadryl and, because of side effects or lack of therapeutic results, were put on Antistine. Many of our other patients, who were on Pyribenzamine or Benadryl for short periods of time, experienced no side effects and had good palliative therapeutic results; they were not included in this study.

It might be well at this time to point out, as shown by Friedlaender and Friedlaender,<sup>4</sup> that although the antihistaminic activity of Antistine, as determined experimentally in the guinea pig, is considerably less than that of Pyribenzamine, we, as well as they, did not find such a discrepancy to be true insofar as clinical effectiveness in allergic conditions is concerned. This would appear to support the contention of many, that histamine plays only a partial role in allergic reactions.

#### SUMMARY

1. Antistine, the trade name for a new antihistaminic manufactured by Ciba, afforded symptomatic relief in a majority of hay fever patients to whom it was given. Such results were less evident, but still present, in many with perennial allergic rhinitis. In asthma, the results were disappointing except for the relief of coughing.

2. In only four cases of urticaria, the results were poor in three cases and good in one case. The drug showed some suggestive effectiveness in two patients with atopic eczema and two with contact eczema.

3. In four cases of allergic conjunctivitis, the results were uniformly good.

4. In two cases of gastrointestinal allergy, one responded very well, and in the other case no effect was observed.

5. The drug was very efficacious in children, because adequate dosage could be given with minimal side effects.

6. It would appear, that 100 mg. of Antistine has roughly the therapeutic effect of 50 mg. Pyribenzamine, with, however, much less side effects.

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# HUNGARIAN MEDICAL TRADE UNION, ASSOCIATION OF PHYSICIANS, SECTION OF ALLERGISTS

Abstracts of lectures presented at the first scientific meeting,  
April 15, 1948

## PROGRESS IN ALLERGIC RESEARCH WORK

### Part I. Theoretical.

By E. RAJKA

A REVIEW of experiments for better definition of allergens, their chemical structure, was given, with special emphasis on the importance of the determining group of complex allergens, as well as the investigation of common group allergens. The limits of sensitization in related chemical substances were emphasized with notes on the pathogenesis of occupational diseases; experimental sensitization may be similar to, or related to, occupational eczema. Complex allergens may be formed in the organism itself.

The structure of reagins is dealt with in experiments (synthetic antibody); reagins seem to be serumglobulins, modified by the effect of chemical configuration and molecule groups of allergens.

The importance of lymphocytes has been emphasized. The most recent passive transfer tests with peritoneal exudates rich in lymphocytes, appearing in infective asthma and experimental eczema (Landsteiner, Chase, Haxthausen) point towards the action of lymphocytes in similar conditions. Kallós thought that the lymphocytes can be transformed into macrophage cells, and therefore belong to the group of macrophages. The problem of thermostable inhibitory substances is touched upon in relationship to the precursory Lechner-Rajka dereagin (Urbach).

### Part II. Clinical

By K. HAJOS

It is emphasized that sensitization and the establishment of local allergic symptoms is possible in every organism, but such local allergic symptoms and experimental results do not coincide with changes in the origin of allergic diseases. Recent research work justifies the importance of heredity and the special reaction of the whole organism beside immuno-biological reactions in the development of allergic diseases. This was called the allergic constitution, allergic diathesis, et cetera. Lately, allergic personality is the term which contains the A and VM groups (Mitchell). The two asthmatic groups prove that immuno-biology cannot explain altogether the origin of asthmatic cases, for if we speak of endogenous, or Mitchell's VM groups in the origin of asthma, we emphasize other factors in its pathogenesis, rather than immuno-biological reactions alone.

It seems to be difficult to diagnose the allergic pathomechanism of bronchial asthma in advanced age, also that of migraine and chronic rhinitis. Purely immuno-biological explanations of conditions lately considered of allergic origin seem to be not quite satisfactory.

Frustrations of World War II, such as changed life conditions, unsatisfactory nourishment, strain and stress, and severe psychic trauma, influenced the appearance of allergic diseases and paroxysms, as well as aggravated or abolished symptoms. Personal investigations seem to differ from those published in the American literature, where depletion, undernourishment, physical and psychic strain and stress of military service, in short—psychic causes, were thought to encourage the appearance of allergic symptoms. In our cases, war conditions, sieges, deportation, life in internment camps and the ghetto, undernourished, brutal and unfair persecution of large social groups established a special physical and psychic environment where constant fear and special conditions diminished the irritability of the central nervous system, the vegetative centers and endocrine functions, and thus abolished excitatory factors evoking allergic reactions. We found that in such severe physical and mental conditions asthmatic attacks, vasomotor rhinitis, urticaria, and giant edema had not been observed. The final cause may be diminished irritability of the hypothalamus and the cortex.

Satisfactory treatment of allergic paroxysms and of asthmatic attacks may be obtained by the aid of psychosomatic medical theory, where the special form of psychiatry is of less importance than effective influence on allergic manifestations.

## BONE MARROW AND ANAPHYLAXIS

By G. FILIPP, A. BAN and L. MATKO

The blood count and myelograms of twenty-four anaphylactic cats were investigated. Ten cats had been sensitized with human serum, the anaphylactic shock being established by re-injection into the saphenous vein. The shock was more intense after rich protein diet. In the peripheral blood count, erythrocytes slightly increased thirty to sixty minutes after the re-injection, while the leukocytes dropped to 50 to 30 per cent of the original number. Leukopenia was followed by corresponding relative lymphocytosis.

First, an increase in eosinophil polymorphonuclear leukocytes, and later in eosinophil staff cells was noted. Two hours after re-injection, neutrophil staff cells increased with a decrease of the same in the marrow, while normoblasts appeared in the peripheral blood after shock. One hour after re-injection, the reaction of the leukopoiesis culminated in the expulsion of mature myeloid cells, and maturation-inhibitory reaction was established in the immature myeloid cells. The latter leads to an increase in immature myeloid cells, such as myelocytes and promyelocytes. There is a rise of lymphocytes associated with that of myelocytes. Increase of

lymphocytes in the marrow is but relative and the total number of myeloblasts does not change.

Metamyelocytes remained unchanged in four cases, they increased in number in three cases, and in three others a decrease was noted. Eosinophil leukocytes disappeared from the marrow during shock and increased on the peripheral circulation. There was a definite increase in lymphoid and plasmocellular reticulocytes of the myelopoietic apparatus at the summit of the reaction, which confirms uniform reaction of the marrow to allergens. Myelopoietic reaction lasts twenty-four hours. Twenty-four hours after re-injection, the peak of erythropoietic reaction is demonstrated by hyperplasia and respective peripheral erythrocytosis. At the height of myelopoiesis and erythropoiesis, we find the greatest number of erythrocyte and leukocyte divisions in the marrow.

By hematological investigations of cats which died in anaphylactic shock, we found leukocytosis and pan-myelophthisis. Inhibition of maturation of leukocytes is being considered as a milder form of pan-myelopathy, compensated by the marrow. After the shock, we always found in the marrow myelocytes with so-called ring-nuclei, which compensated in our cases for the maturation-inhibitory effect. As the center of the myelocytic nucleus dissolved, the ring grew gradually thinner, later it broke up, and myelocytes matured to staff form without passing the metamyelocytic stage.

Ten cats were re-injected immediately into the marrow after sensitization. Peripheral changes were as follows: erythrocytes, neutrophil leukocytes, lymphocytes and staff cells did not change in number; eosinophil leukocytes disappeared from the peripheral blood. Changes in the marrow were: culmination of myelopoiesis in one hour; that of the erythropoietic reaction four hours after re-injection with very pronounced local eosinophilia with peripheral eosinophilopenia pointing towards migration to the marrow.

In four cases, agranulocytosis was established by means of allergic reactions. It is certain that the eosinophilia derives from the bone marrow.

#### DISCUSSIONS

L. MOSONYI: Years ago M. investigated differential blood count and myelogram in aspirin and barbiturate poisoning. He found the most prominent changes to be "shift to the left," mild leukocytosis, increase in number of immature cells in the marrow, all appearing by milder poisoning, while no change was seen in the beginning by other groups. In very mild cases, there had been no other changes, while in very severe cases the normal blood count was regained through the moderate severe cases. This may be explained by shock-effect, after which the reaction of the marrow can be established alone.

K. HAJOS: Discussion of exact hematological experiments confirmed earlier investigations, showing that the eosinophilia observed in allergic-

anaphylactic reactions originated from the fact that eosinophil leukocytes are being formed in the bone marrow, and wander to the site of allergic and anaphylactic reactions. Local eosinophilia may be explained by substances formed during localized immuno-biological reactions. Earlier experiments proved that in the peripheral blood the number of eosinophil leukocytes showed a periodical change with increase before the attack, followed by peripheral decrease, as well as local accumulation and sometimes excretion.

## INFLUENCE OF THE AUTONOMIC NERVOUS SYSTEM ON THE ESTABLISHMENT OF SERUM-SICKNESS

By L. LENGYEL

The state of the autonomic nervous system of forty-nine patients suffering from diphtheria, and inoculated for the first time, was studied after intravenous injection of 0.01 mg. of epinephrine.

1. All patients showing increased vagotonia had serum-sickness of longer duration with more severe clinical symptoms than in those whose autonomic nervous system was well balanced. Difference of the two groups was significant.

2. Incubation time showed no prominent difference between the two groups.

It was concluded that the state of the autonomic nervous system is an important disposing factor in the origin of serum-sickness. Its effect lies less in reagin formation than in its influence on the symptoms established by tissue cells during the allergin-reagin reaction.

3. Increased sympathetic tone diminishes susceptibility to diphtheria.

## CRYMOTHERAPY AND ANAPHYLAXIS

(Continued from Page 668)

### SUMMARY

Refrigeration in guinea pigs appears to slow the onset of anaphylactic symptoms. It prevented fatality, however, in only 38 per cent of the test animals, a figure not considered significant. It did not prevent the onset of signs of anaphylaxis in any of the animals. It seemed to delay the onset of signs of histamine shock, without preventing fatal shock.

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# EVALUATION OF THERAPEUTIC SUBSTANCES EMPLOYED FOR THE RELIEF OF BRONCHOSPASM

## II. Historical Development and Methods

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THE search for a common substance active in the protean manifestations of allergy and anaphylaxis in animals and man has involved many investigators and countless studies over the past four decades. In these varying and conflicting reports, two substances, histamine and acetylcholine, have often been considered possible chemical mediators of allergic phenomena. Both of these substances are capable of producing dyspnea and bronchospasm in asthmatic subjects and may be used in the evaluation of agents capable of protecting against these effects. With this technique a method of assay in humans of the relative value of new and of accepted therapeutic agents for the relief of bronchial asthma has been evolved. The development and present status of this technique is the subject of this report.

### HISTAMINE

Histamine (beta-iminazolyethylamine) was recognized among the active amines of ergot by Barger and Dale in 1910.<sup>5</sup> In the same year, Ackermann<sup>1</sup> demonstrated that the normal bacterial flora of the intestinal tract produced large amounts of the same compound by the decarboxylation of histidine. Dale at once began investigations on the possible physiological role of this substance and concluded that "the immediate symptoms of poisoning by beta-iminazolyethylamine . . . are to a large extent those with which an animal responds to an injection of . . . normally inert protein to which it has been sensitized."<sup>21</sup>

Thus, within a year after histamine was first noted to be a pharmacologically active material, and long before it was demonstrated to be present in mammalian tissues (Best et al, 1927<sup>8</sup>), the striking similarity between the effects of administered histamine and the phenomena of anaphylaxis in animals was observed. However, Dale, together with most subsequent investigators, carefully refrained from assigning a causal role to histamine in this situation.

Much evidence bearing on the possibility that histamine formation or release is the basic mechanism in allergic and anaphylactic phenomena has been accumulated. The evidence for such a concept has been summarized by Dragstedt<sup>33,34</sup>: (1) As originally noted by Dale, the effects following the administration of histamine are similar to anaphylactic shock;<sup>21</sup> (2) histamine is present in mammalian tissues in concentrations quantitatively sufficient to explain the phenomena of anaphylaxis on the basis of released histamine;<sup>78,62,35,36</sup> (3) allergic manifestations in man are similar to the effects of administered histamine;<sup>33</sup> (4) a histamine-like substance is actually released during allergic states in man;<sup>34</sup> (5) antihistaminic agents clinically may be used for the control of many symptoms of allergy.

These similarities of action form the basis for the widely accepted view that histamine is an important agent in allergic conditions. However, this belief is not universal. Wells, in 1921<sup>82</sup>, found certain discrepancies between histamine and anaphy-

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lactic shock: histamine fails to desensitize animals or tissues, although it does produce strong reactions in the uterine muscle strip which has been desensitized; it produces neither the temperature reactions nor the changes in blood coagulability seen in anaphylaxis; and its effects are not augmented by quinine, whereas those of anaphylaxis are. In turn, these and other objections have been answered in great detail by proponents of the histamine theory. The literature in this regard is voluminous and has been completely reviewed by various authors.<sup>62,9,60,71</sup>

The bronchospastic potentialities of histamine were recognized by the earliest investigators,<sup>21</sup> but it was not until 1921 that Schenk<sup>64</sup> demonstrated respiratory distress, attributed to broncho-constriction, after administration of large doses of this agent. In 1927, Weiss, Robb and Blumgart<sup>79</sup> studied the velocity of the circulation of the blood in man by means of injections of histamine. In the course of this work they induced dyspnea, with the signs and symptoms of bronchial asthma, in several subjects with a past history of asthma. They likewise induced dyspnea in patients suffering from chronic bronchitis, emphysema, or cardiac asthma, as well as in a few individuals with congestive heart failure. The definite bronchospastic action of histamine in such individuals was confirmed in another study by Weiss, Robb and Ellis.<sup>80</sup> This bronchospastic action of histamine in individuals with various types of respiratory disease has been used diagnostically as a "respiratory function test" by Schlösser<sup>66</sup> and Müller<sup>53</sup> in differentiating varieties of dyspnea.

Dautrebande and his co-workers in Europe have long been interested in the aerosol route for topical application of therapeutic substances to the inner surface of the lungs and, by means of bronchopulmonary absorption, to the general body economy. In 1940 they used histamine aerosols to demonstrate the possibility of this transpulmonary absorption,<sup>23</sup> and, in the following years, they studied in great detail the action of aerosolized histamine upon the lungs.<sup>24,25,26</sup>

Dautrebande's complex techniques for aerosol production and administration and his methods of measurement of pulmonary function differ from those we have used. He finds that three inhalations of a 1 per cent histamine aerosol, as produced in his apparatus, lead to an increase in the efficiency of respiration and in "pulmonary volume," namely, to bronchial relaxation. On the contrary, we have produced, in occasional subjects, a significant drop in vital capacity with only one inhalation of a hand-bulb-produced aerosol of a 0.5 per cent solution of histamine base. Three inhalations of this solution will produce bronchospasm in many of our subjects.

Curry, in 1946,<sup>17,18</sup> administered histamine diphosphate by intravenous and intramuscular routes both to normal subjects and to those suffering from hay fever and asthma. The resulting changes in respiratory function were measured and determined as alterations in the vital capacity. He found that histamine in the doses employed produced no significant drop in vital capacity in normal subjects or in hay fever patients, but it did cause significant decrease in vital capacity in most asthmatics.

If histamine is the offending agent in allergic reactions, then, theoretically, it might be possible to use it in minute and gradually increasing doses in the same manner as allergenic extracts are used, namely, as a therapeutic hyposensitization measure. Favorable results from such an approach to the treatment of asthma were reported by Ramirez and St. George in 1924,<sup>61</sup> Dzinich in 1935,<sup>37</sup> Farmer in 1940<sup>41</sup> and 1941,<sup>42</sup> and others. However, the apparent lack of success with this preparation in the hands of most investigators led to the subsequent use of histamine-protein conjugates; these, too, are now thought to be essentially valueless.<sup>43</sup>

Histamine is destroyed *in vitro* by various tissue extracts which have been considered to contain histaminase, an enzyme which, too, has been suggested as a therapeutic possibility; it has also been found largely inert clinically.<sup>16</sup> Best, who originally described this enzyme, feels that his group and other workers "have failed to show that the intravenous or intramuscular administration of histaminase has any effect on the histamine present in the body or on that given by injection."<sup>10</sup>

## ACETYLCHOLINE

Acetylcholine, synthesized by Baeyer in 1867, came into experimental and clinical use as a result of the demonstration by Loewi of its role as the chemical mediator of vagal impulses ("Vagusstoff")—at least as far as the heart was concerned.<sup>52</sup> Acetylcholine shares certain physiological properties with histamine: it is widely distributed in living tissues; it is the acetyl ester of a base (choline) and is thus chemically, though distantly, related to histamine, also an organic base; and it is, as histamine has been thought to be, destroyed *in vivo* by an enzyme, cholinesterase. The action of cholinesterase may be prevented by physostigmine (eserine) or its derivative (e.g. neostigmine). While the physiological role of histamine remains obscure, acetylcholine has a vital function in the normal organism. It is the chemical mediator of nervous impulses across synaptic junctions in the entire nervous system, and it also serves as the chemical mediator effecting the passage of nervous impulses from motor nerve endings to effector organs in the parasympathetic nervous system as well as in the central nervous system.

In general, the actions of acetylcholine may be divided into those which are similar to the effects of stimulation of the parasympathetic nervous system (which may be simulated by muscarine) and those occurring within ganglia and at the motor end-plates of striated muscle (similar to the effects of nicotine). The muscarinic actions of acetylcholine can be prevented or blocked, to a large extent, by atropine; the nicotinic effects can not. Administration of acetylcholine to man leads to phenomena largely of the muscarinic type: flushing of the head and upper part of the body, throbbing in the head, palpitation, sweating, lachrymation, substernal constriction, and, when given in larger doses, to nausea and vomiting and loss of urinary and rectal sphincter control. The intravenous administration of moderate doses of acetylcholine has little or no effect on pulse and blood pressure;<sup>39</sup> larger doses produce bradycardia and hypotension.<sup>14</sup>

Acetylcholine is a markedly unstable compound, and is itself seldom employed clinically. Two derivatives are available, carbaminoylcholine and acetyl-beta-methylcholine. The latter is more usually employed as a parasympathomimetic agent. It produces effects closely similar to but not identical with those of acetylcholine.<sup>15</sup> So far as cardiovascular and general responses are concerned, acetyl-beta-methylcholine is 200 times more potent than the parent substance.<sup>8</sup> The relationship of these substances to one another and to the transmission of the nervous impulse is the subject of a series of Croonian lectures by Fraser.<sup>44</sup>

The first suggestion that bronchial asthma might represent an imbalance of the autonomic nervous system with an abnormal preponderance of vagal impulses was made in 1909 by Eppinger and Hess,<sup>40</sup> who characterized asthma as an example of "pathological vagotonia." In 1921 Alexander and Paddock<sup>3</sup> afforded some support to this theory. They found that patients with bronchial asthma were more sensitive to pilocarpine, a drug which simulates the action of the parasympathetic nervous system, than were normal individuals. In addition, the administration of 3 mg. of pilocarpine subcutaneously provoked asthmatic breathing in ten of twenty asthmatic subjects, whereas it had no such effect in normal subjects.

While studying the effects of intravenous administration of acetylcholine to normal men, Ellis and Weiss in 1932<sup>39</sup> found that "frequently the subjects experienced a sensation of substernal constriction with some difficulty in inspiration and a slight dry cough. No true wheezing was noted." These findings were confirmed for acetylcholine by Carmichael and Fraser,<sup>14</sup> and for acetyl-beta-methylcholine by Comroe and Starr.<sup>15</sup> In the course of further studies with acetyl-beta-methylcholine, Starr et al, in 1933,<sup>32</sup> found that in one subject with a history of asthma, parenteral administration of this agent led to the development of "a typical asthmatic attack" lasting three minutes. Similar but milder episodes were produced in other known asthmatics after oral administration of acetyl-beta-methylcholine, as well as in one elderly patient



not previously known to have bronchial asthma.<sup>73</sup> In the next year, Villaret and his co-workers<sup>76</sup> reported bronchospasm and rhinorrhea in asthmatics induced by the subcutaneous administration of 20 to 40 mg. of acetyl-beta-methylcholine. These episodes, some of which were quite severe, could be terminated at will by atropine. It is noteworthy that coryza could not be reproduced in a patient with allergic rhinitis. No similar respiratory effects were noted after the administration of these doses of acetyl-beta-methylcholine to normal individuals. Villaret's group was sufficiently impressed with these phenomena to recommend the use of acetyl-beta-methylcholine as a diagnostic test in differentiating bronchial asthma from hysterical hyperpnea. Simultaneously, Hurtado and Kaltreider,<sup>47</sup> studying the total pulmonary capacity, induced decreases in vital capacity of 700 and 760 c.c. after administration of 15 and 30 mg. of acetyl-beta-methylcholine intramuscularly to two healthy young adult subjects. These decreases in vital capacity were associated with substernal constriction and difficult breathing.

This gradually accumulating body of evidence, tending to involve acetylcholine as the chemical mediator of allergic as well as of nervous phenomena, led to the study by Wenner and Buhrmester of the level of acetylcholine in the blood of rabbits in anaphylactic shock.<sup>83</sup> These investigators showed that acetylcholine was present in the blood of sensitized and of shocked rabbits, although it was not found in normals. Physostigmine was not used, and the demonstration of acetylcholine in blood when cholinesterase activity has not thus been eliminated must mean that higher levels were actually present. The presence of histamine in the blood of similarly prepared animals has also been demonstrated, but the results are conflicting.<sup>78,62,35,36</sup> Alexander, discussing the paper of Wenner and Buhrmester,<sup>83</sup> felt that all the peripheral manifestations of anaphylaxis and allergy might be reproduced by stimulation of the parasympathetic nervous system. The results of this investigation were confirmed in human asthmatics by Parrot.<sup>59</sup> Fraser<sup>44</sup> reported definite, fluoroscopically observed, constriction of the smaller bronchi when 25 mg. of acetyl-beta-methylcholine were administered intramuscularly in the course of bronchography with iodized oil.

In 1940, Moll<sup>57</sup> carefully studied the effect of the subcutaneous administration of acetyl-beta-methylcholine in asthmatic subjects. To quote Moll, "the attack produced by acetyl-beta-methylcholine is indistinguishable from a spontaneous attack of asthma." Using doses of 10 to 20 mg., he was able to produce some degree of bronchospasm in almost every asthmatic patient; very few normal subjects experienced any disturbance of respiratory function after such injections. Moll felt that in asthma "it is the bronchial nervous system which is abnormally sensitive and not the whole parasympathetic nerves (*sic*) as Eppinger and Hess maintained in their theory of vagotonia."<sup>47</sup> He believed that this abnormal hypersensitivity of the bronchial tree to vagal impulses was the result of previous lung damage that might have occurred in cases of asthma following pneumonia, pertussis, et cetera. Villaret et al,<sup>77</sup> in animal experiments, found that the susceptibility of the tracheobronchial tree to carbaminoylcholine was greatly increased by inhalation of irritant vapors.

Moll refrained from assigning acetylcholine a causal role in bronchial asthma because atropine, which effectively antagonizes the effects of administered acetylcholine on the bronchial tree, is of limited clinical value in the treatment of asthma.<sup>57</sup> This apparent paradox has been noted in other experiments on the parasympathetic nervous system. Dale and Gaddum in 1930<sup>22</sup> found that the blocking action of atropine upon the muscarinic effects of acetylcholine existed in three degrees. In some cases it was complete; in others, the effects of administered acetylcholine could be prevented while those of nerve stimulation were not affected; and in still other instances, atropine apparently had no blocking effect whatever. Such phenomena have been observed in the gastrointestinal tract, in the tissues innervated by the parasympathetic fibers of the chorda tympani, and in the contracture of denervated striated muscle after stimulation of parasympathetic vasomotor fibers. It was postulated that the

action of atropine might be considered as producing a barrier preventing the access of acetylcholine to the effector organ. The effect of atropine will then vary as the acetylcholine is liberated outside, partly within, or wholly within this barrier. Despite the lack of clinical efficacy of atropine, it is thus possible that acetylcholine may be the agent responsible for the bronchospasm of bronchial asthma.

In this connection, the effect of atropine on anaphylactic shock is of importance. However, this a debatable subject. Hill and Martin,<sup>40</sup> in their classic review of experimental studies of nonspecific inhibition of anaphylactic shock, list atropine as one of the eighteen substances which had been shown to have a definite inhibitory action on anaphylactic phenomena. Kokas et al<sup>48</sup> were later unable to confirm this view.

While working with dogs prepared so that the trachea was interrupted and respiration took place through a tracheal cannula, Binet and Burstein in 1940<sup>11</sup> found that irritation of the nasal mucosa by fumes of ammonia, which did not come into contact with the trachea or lower respiratory passages, led to marked constriction of the bronchi and bronchioles. This reflex was exaggerated by physostigmine and was abolished by section of the vagi. This demonstration of one type of bronchospasm, definitely of reflex vagal origin, lends collateral support to the acetylcholine theory of the pathogenesis of asthma. A more complete study of the nasal passages is included in a report on the etiology of dyspnea in the hay fever patient.<sup>6</sup>

The bronchospastic potentialities of choline derivatives have been further investigated by Dautrebande and his group in their continuing study of the properties of various aerosols.<sup>24,26,27,62</sup> They have been particularly interested in the effects of aerosols of solutions of carbaminoylcholine. This has become their standard method for the production of bronchospasm, which they have been able to neutralize by injections of atropine and by aerosols of amphetamine. Dautrebande and Phillipot in 1941<sup>28</sup> further demonstrated that the administration of amphetamine will protect a human subject against the bronchospastic action of a subsequent dose of carbaminoylcholine aerosol.

Tiffeneau and Beauvallet in 1944<sup>74</sup> and 1945<sup>75</sup> demonstrated that inhalation of 1 per cent acetylcholine aerosol produces no modification of respiration in a normal subject; but in individuals with respiratory insufficiency, it provokes a diminution of vital capacity of 700 to 1000 c.c., even when the patient is asymptomatic and when other tests reveal no evidence of disability. They suggested that this response might be used diagnostically and as a measurement of the degree of disability from which a given subject might be suffering. They were able to show that acetylcholine administered in this way is totally destroyed in the lung and thus produces no systemic effects, thereby rendering their proposed test a fairly innocuous one.

Curry in 1947<sup>18</sup> reported the effect of intravenous and aerosol administration of acetyl-beta-methylcholine on the vital capacity of both normal subjects and patients with hay fever and asthma. He was able thus to produce decreases in vital capacity in eleven patients with hay fever and in twenty-seven with asthma. Normal subjects did not respond.

As with histamine, attempts have been made to treat allergic individuals by graded injections of acetyl-beta-methylcholine. Logue and Laws in 1942<sup>53</sup> reviewed the previous literature and presented their own experiences with twenty patients. They concluded that such therapy was of no material benefit.

The possible role of cholinesterase in the pathogenesis of bronchial asthma requires further study. A few isolated observations of Millhorat<sup>56</sup> indicate that the level of serum cholinesterase in asthmatics may be higher than normal. This would seem to lead to more rapid destruction of acetylcholine than normal, and thus, toward bronchial relaxation rather than asthma. Cholinesterase has not been available for therapeutic trial in asthmatic patients.

# EVALUATION OF THERAPEUTIC SUBSTANCES—LEVINSON ET AL

## HISTORICAL DEVELOPMENT OF PROTECTION STUDY TECHNIQUES IN THE INVESTIGATION OF BRONCHOSPASM

From the time of the first data linking the manifestations of allergy in man to those of anaphylaxis in animals, many investigators have attempted to find experimental procedures or therapeutic substances which might modify anaphylactic reactions and thus be of clinical value in the treatment of the allergic patient. In 1932, Hill and Martin<sup>46</sup> reviewed over 150 such techniques, ranging from adrenalectomy to the use of mud from therapeutic springs. Epinephrine and atropine were among the substances which these authors felt were of value in inhibiting anaphylactic shock; quinine was thought to intensify such phenomena. Edlbacker, Jucker and Baur in 1937<sup>48</sup> investigated the protecting ability of various amino acids against the effect of histamine on guinea pig intestinal strips *in vitro*. They found histidine, arginine, and cysteine to be active in this regard. Tremendous doses are necessary, however, and these compounds are of little clinical value as antihistaminic agents. Ackermann and Wasmuth in 1939<sup>2</sup> confirmed these studies and added several new protecting agents, derivatives of arginine and guanidine. Again, toxic doses were necessary, but these authors were able to protect dogs against the hypotensive effects of subsequently administered histamine with some of their compounds. No action against acetylcholine could be demonstrated.

Binet and Bochet in 1941,<sup>12</sup> using aerosols, were able to protect dogs against the bronchospastic effects of histamine and of carbaminoylcholine with aerosols of epinephrine; aerosols of atropine also relaxed the spasm induced by carbaminoylcholine. Halpern<sup>45</sup> investigated the antihistaminic agent N'-phenyl-N'-benzyl-N-dimethylethylenediamine (Antergan) in 1942. Pre-treatment of guinea pigs with this substance prevented the occurrence of asphyxia after subsequent exposure to histamine aerosols. Schaumann<sup>63</sup> in 1943 devised a standard technique (in terms of the latent period of development of bronchospasm after exposure to histamine aerosols) for measuring the protecting effect of various agents against histamine-induced bronchospasm in guinea pigs. He found this time interval (standard protection time) to be prolonged by various ephedrine and epinephrine derivatives, of which dihydroxyephedrine was the most potent. Atropine and papaverine were inert.

In 1945 and 1946, Loew, Kaiser and More<sup>49-51</sup> studied extensively the protecting effect of various drugs against atomized histamine in guinea pigs. They devised a technique by which 90 to 100 per cent of experimental animals succumbed to asthma induced by the inspiration of atomized histamine solutions in closed chambers. They then tested the ability of various drugs to protect against this bronchospasm by intraperitoneal administration fifteen minutes prior to exposure of the animals to the histamine spray. Various agents provided significant reduction of mortality. Loew et al proposed an "activity index" for the description of the relative antihistaminic potency of these substances. This index denotes the ratio of the minimum dose of the drug in question exhibiting a significant protecting action to the dose of theophylline ethylenediamine which produces the same effect. Thus aminophyllin has an index of 1.0. Epinephrine with an activity index of 500 was the most potent agent employed; diphenhydramine hydrochloride (Benadryl) with an index of 33, meperidine hydrochloride (Demerol hydrochloride) with an index of 8, atropine sulfate with an index of 3, and papaverine hydrochloride with an index of 2, also provided significant protection. Many substances had no protecting action; these were 2-amino-heptane sulfate (Tuamine sulfate), beta-diethylaminoethyl diphenyl acetate hydrochloride (Trasentin), beta-diethylaminoethyl fluorene-9-carboxylate hydrochloride (Pavatine), gamma-diethylamino-beta, beta-dimethylpropyl-dl-tropate phosphate (Syntropan), procaine, 2-butoxy-4-(beta-diethylaminoethylamido) carboxyquinoline hydrochloride (Nupercaine), pentobarbital, morphine and ergotamine. Perplexingly, ephedrine, as well as physostigmine, seemed to potentiate this experimental asthma. The paradox-

ical action of ephedrine was assigned to its stimulating effect on respiration, resulting in the inspiration by the guinea pigs of more of the histamine spray, and thus producing more severe bronchospasm than was provoked in the control animals. The lack of similar potentiation of bronchospasm by caffeine sodium benzoate, an even more powerful respiratory stimulant, is as yet unexplained. The potentiation with physostigmine "may be referable to the potentiation of the systemic effects of acetylcholine which would be liberated in increased quantities during asphyxial convulsions."<sup>50</sup>

Simultaneous with these pharmacological studies, Dautrebande and his collaborators <sup>26,27,31,32</sup> demonstrated the protecting ability of intravenous atropine against aerosols of carbaminoylcholine in dogs and the similar protecting action of amphetamine aerosols in human subjects. By 1942, these investigators had studied a long series of bronchospastic and bronchodilator substances and had demonstrated the antagonistic and protecting actions of each class of drugs on the other. They have employed the following bronchodilator agents (in order of increasing potency): epinephrine, dioxy-norephedrine (Corbasil), paraoxyphenylethanolmethylamine (Synephrin), oxyphenylaminopropane (Veritol), ephedrine, alphas-hydroxy-beta-methylaminopropylbenzene (Ephedrine), oxyephedrine (Suprifen), benzyl ether of benzylethylmethylamine (Arlin), phenylmethylaminopropane (Pervitin), phenylaminopropane (amphetamine), meta-oxyphenylethanolmethylamine (Neo-Synephrine), and isopropylphenephrine (Aleudrin or Isuprel). Segal and Beakey <sup>67,68</sup> were the first in this country to describe the clinical value of Isuprel. Atropine aerosols of themselves were found to have little action in normal subjects, but were very efficacious in releasing the bronchoconstriction produced by aerosols of pilocarpine or of choline esters. Dautrebande and his associates have made use of carbaminoylcholine and, to a lesser extent, of histamine, pilocarpine, acetyl-beta-methylcholine and acetylcholine itself<sup>29</sup> as bronchospastic agents.

Tiffeneau and Beauvallet,<sup>75</sup> in their study of the use of aerosols of acetylcholine to measure the degree of respiratory insufficiency in disabled individuals, made use of the complete protecting effect of atropine aerosols against acetylcholine in the detection of malingerers, who might then react to subsequent acetylcholine aerosols, whereas truly asthmatic individuals would not.

Curry, in 1946,<sup>19</sup> using serial determinations of the vital capacity as a measure of bronchoconstriction, as did Hurtado and Kaltreider,<sup>47</sup> studied the protecting action of various substances on the bronchospasm produced in asthmatic subjects by intravenous administration of histamine. He investigated diphenhydramine hydrochloride (Benadryl), tripelemamine hydrochloride (Pyribenzamine), atropine, aminophyllin, epinephrine, and ephedrine. Both of the antihistaminic agents studied were found to have protecting ability against histamine. Atropine, too, was found to furnish complete protection against the bronchospasm produced by aerosols of histamine (one experiment), but it protected only partially against histamine administered intravenously. Theophylline ethylenediamine furnished "prompt and potent protection against the tracheobronchial effects of intravenous histamine."<sup>19</sup> Epinephrine and ephedrine administered intramuscularly were also effective against histamine. Curry concluded that "this method of study provides a means of measuring the bronchodilator activity of the various sympathicomimetic amines."<sup>19</sup> His technique yielded results in which data on individual patients could not be massed into statistically significant forms, and thus accurate comparison of various antihistaminic agents was not practicable.

As interest in the laboratory production of bronchospasm in susceptible individuals has grown, attempts have been made to induce such bronchospasm by means of allergens, and to avoid the controversial nature of the effects of histamine and of the choline esters. Lowell and Schiller<sup>54,55,55</sup> have recently demonstrated decreases in vital capacity in sensitive asthmatics after the administration of aerosols of pollen extracts. This and similar techniques give great promise for the future.

We have modified the techniques described above so that statistically valuable data may be produced and various agents used in the treatment of asthma be assayed.<sup>60</sup> We have employed, by aerosol as well as intravenous routes, histamine, acetyl-beta-methylcholine, and allergenic extracts as bronchospastic agents. Results obtained from the study of the first group of agents tested (parasympatholytic substances) follow;<sup>7</sup> other reports are in preparation.<sup>13,70</sup> By means of this technique, we hope that an approach may be made to the fundamental problem of the pathogenesis of bronchial asthma and thus to its management on a rational basis.

#### METHODS

Various methods for measuring different aspects of pulmonary function have been used, such as measurement of reserve air, inspiratory and expiratory velocities, total pulmonary ventilation, and determination of vital capacity.<sup>20</sup> We have employed the last named method in the majority of our studies, and it has proved entirely adequate for our purposes. It is a simple procedure that requires no complicated apparatus or time-consuming calculations. A modification of the standard Benedict-Roth spirometer with a rapidly moving drum, equipped with a Reichert counter, was employed in many of the studies. In others, we employed the easily portable McKesson-Scott vital capacity apparatus, which is particularly useful when more than one subject is being studied at one time. Vital capacity determinations with either apparatus are identical.

Certain factors, including age, cough, general weakness, state of dentition, emotions, intelligence and co-operation, make widely separated determinations of vital capacity entirely unreliable. However, co-operative subjects can be trained to repeat vital capacity determinations which fall consistently within a relatively narrow range. It was usually possible, without undue selection of individuals, to train our asthmatic subjects so that decreases resulting from the administration of bronchospastic agents could be adequately evaluated. A further training period was necessary so that the subjects would be able to concentrate upon the expiratory effort of the vital capacity determination to the exclusion of the sometimes disturbing side reactions produced by administration of these agents. Side effects varied with the route of administration: intravenous injection produced the severest reactions; intramuscular administration, less intense but more prolonged reactions; and the aerosol route, only rare and slight reactions.

The intravenous route, as compared with the intramuscular, is more quantitative, constant, and predictable, and is therefore preferable.

The effect of intravenous administration of histamine or acetyl-beta-methylcholine begins fifteen or twenty seconds after its administration. The first effect is that of a disagreeable metallic taste (this sensation of taste makes positive that the injection was intravenous), accompanied by the beginning of a series of sensations related to vasodilatation and other cardiovascular phenomena. These responses reach their maximum in approximately forty-five to sixty seconds and consist of headache, flushing, palpitation and giddiness. Administration of acetyl-beta-methylcholine often produced salivation, lacrimation, and a sense of substernal constriction, whereas headache was not noted. Serial determinations of the vital capacity after the administration of either of these agents revealed that the maximum diminution in vital capacity occurs approximately thirty seconds after the intravenous administration of the bronchospastic substance. This drop was determined with stopwatch timing by having the patient perform vital capacities at specified intervals after injection. The most satisfactory intervals were found to be thirty seconds and then one, two, three, and five minutes after injection. We have repeatedly shown that a patient is capable of performing vital capacities at thirty second intervals for several minutes without appreciable change. As previously noted, the maximum drop in vital

capacity is almost invariably seen thirty seconds after injection. Figure 1 depicts a typical response to the intravenous injection of a bronchospastic agent. The vital capacity usually returns to normal in one to five minutes; frequently, it returns to levels considerably higher than the original. This "rebound phenomenon" will be discussed

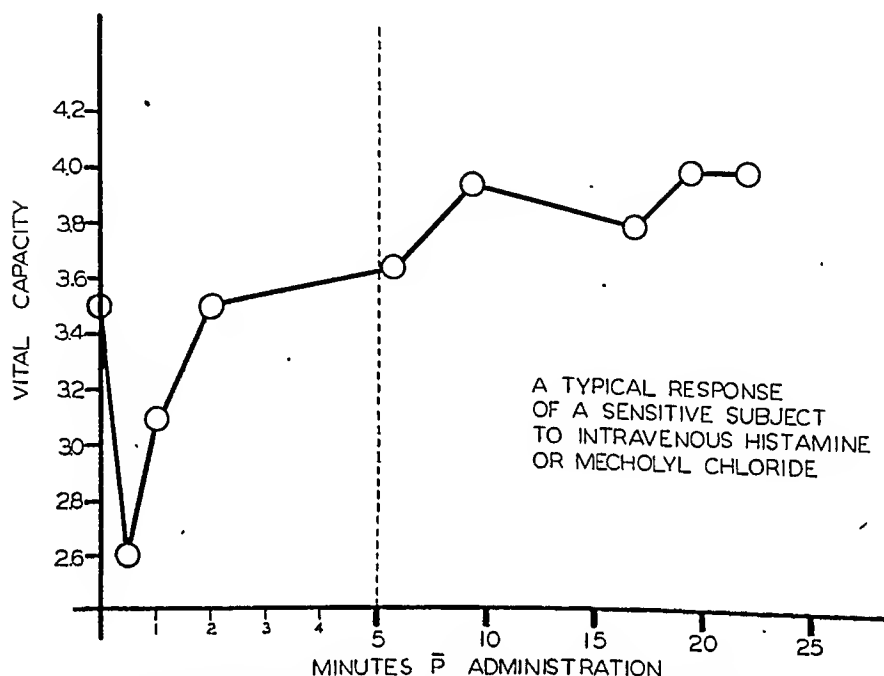


Fig. 1. A typical response of a sensitive subject to the intravenous administration of histamine or acetyl-beta-methylcholine.

below. After pre-treatment of the experimental subject with protecting agents, the return of the vital capacity to the resting level after injection of the bronchospastic substance was usually more rapid.

Histamine diphosphate solution (Abbott),\* of which each c.c. represented 0.1 mg. of histamine base, was used. All doses of histamine are reported in terms of the base. The preparation of acetyl-beta-methylcholine chloride was that of Merck\*\* (Mechoylchloride) and hereinafter will be referred to simply as "mecholy." It was dissolved in sterile physiological saline to a final concentration of 1.0 mg. per c.c. (doses of this substance are reported in terms of the chloride). The concentration of each substance was chosen so that the usual dose for intravenous administration would fall within the range of 0.1 to 0.4 c.c., and thus a quick and accurately timed injection was made possible. Fresh solutions of mecholy, stored in sterile rubber-capped vials and refrigerated when not in use, were prepared weekly. The marked instability of the choline ester linkage makes such precautions necessary. It is an accepted fact that the blood cholinesterase rapidly inhibits the action of administered acetylcholine. This suggested the possibility that drawing blood back into the syringe prior to intravenous injections might lead to the destruction of some of the mecholy. Consequently, tests were performed in which the amount of mecholy known to cause a drop in vital capacity was mixed with the patient's blood for ninety seconds and then reinjected. No alteration in the previously determined drop in vital capacity

\*Kindly supplied through the courtesy of Abbott Laboratories, North Chicago, Illinois.

\*\*Kindly supplied through the courtesy of Merck and Company, Rahway, New Jersey.

occurred, and it was apparent that immediate hydrolysis by the esterase was not sufficient to alter the studies in question.

New patients generally first received intramuscular injections of 0.06 mg. of histamine or 0.1 mg. of mecholyl as test doses in order to detect any abnormal sensitivity; no such instance was demonstrated. The intravenous doses of histamine usually ranged from 0.01 to 0.04 mg. However, two subjects reacted consistently to 0.005 mg., and one subject to 0.002 mg. The highest dose used in a protection study has been 0.06 mg., although greater amounts have been administered during the course of our investigations. In general, a dose of mecholyl sufficient to produce a significant drop in vital capacity was attended by much less severe side effects than an equally effective dose of histamine. The doses of intravenous mecholyl employed usually ranged from 0.05 to 0.4 mg. Sometimes the severity of the side reactions produced by histamine necessitated discontinuing the experiment before a dose capable of producing a decrease of the vital capacity could be given. Side reactions to mecholyl were much better tolerated. Occasionally the critical range of bronchospastic doses was very narrow and resulted in the administration of excessive amounts even with very small increments. The most prominent symptom from overdoses of histamine usually was incapacitating headache. However, excessive doses of mecholyl produced more alarming effects. Approximately twenty-five seconds after such an injection the patient seemed to lose consciousness. A vacant stare appeared, followed by momentary cessation of respiration and clonic movements of the arms and legs. The entire reaction lasted only ten to fifteen seconds. A solution of atropine sulfate was always kept ready, in a syringe, for immediate intravenous administration, but no reaction long enough to allow its use occurred. Patients later described such reactions as "going numb all over" with a sense of constriction in the chest and transitory inability to move the limbs. The clinical features of these reactions suggest transitory asystole.

The aerosol route for administration of bronchospastic agents, and of therapeutic substances as well, has been employed extensively. In all instances we have made use of aerosols produced with the standard Vaponefrin<sup>†</sup> nebulizer. For uniformity, a standardized technique for aerosol administration has been devised. The nebulizer is held by the experimenter with its outlet orifice close to the patient's open mouth. The experimenter counts aloud, and at the count of "three" the nebulizer bulb is squeezed with maximal force as the patient simultaneously makes the deepest and most rapid inspiration possible, following which he holds his breath in inspiration for four or five seconds. The procedure is repeated at precisely ten-second intervals, until the desired number of inhalations has been given. The stopwatch is then immediately reset; further time intervals are thus calculated from the end of the last inhalation.

In contrast to the sequence of events following intravenous administration of histamine and of mecholyl, the effect of such agents given by the aerosol route is slower both in onset and in recovery. The maximum drop in vital capacity usually occurs one or two minutes after the last inhalation; in occasional instances it may not take place until three minutes thereafter. Recovery is usually complete within eight to ten minutes. A typical response of a sensitive subject to an aerosol of a bronchospastic agent is depicted in Figure 2. We have not observed the "rebound phenomenon" following the administration of histamine or of mecholyl by the aerosol route. Side-reactions are infrequent when bronchospastic agents are administered in this way, in contrast to their almost invariable occurrence, to some degree, after intravenous injection. Those side-effects which do occur are similar to the reactions already described, but much less severe.

Essentially, a protection study consists of the determination of the effect on vital

<sup>†</sup>Kindly supplied through the courtesy of the Vaponefrin Company, Upper Darby, Pennsylvania.

capacity of a bronchospastic agent before and at varying intervals after administration of a protecting drug.

A typical protection study was begun with a rest period of fifteen to twenty minutes; the patient sat quietly, and all constricting clothing was loosened. The vital

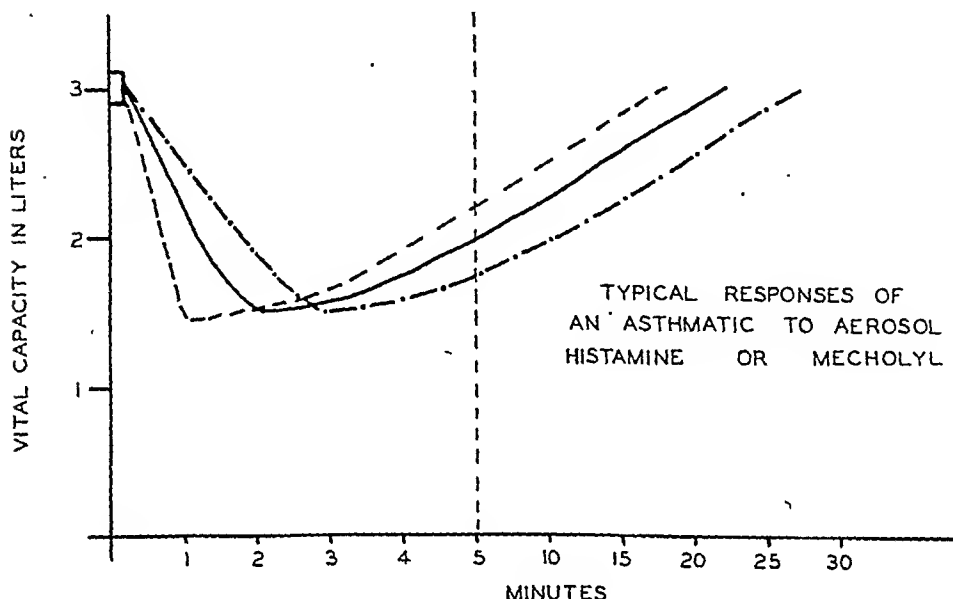


Fig. 2. Typical responses of asthmatic subjects to the administration of aerosols of histamine or acetyl-beta-methylcholine.

capacity was determined serially until several results were, within plus or minus 100 c.c. The dose of bronchospastic agent required to produce a significant "control" drop in vital capacity was then determined. Such a significant drop was usually 1 to 2 liters, although sometimes it was necessary to accept slightly smaller decreases in those patients whose basal vital capacities were as low as 2 liters. In this determination, gradually increasing amounts of bronchospastic agent were administered every twenty to thirty minutes until a desirable decrease in vital capacity was obtained. In the case of histamine, the increments were 0.005 or 0.01 mg., and, in the case of mecholy, 0.05 or 0.1 mg.

After the control drop for the day was established and verified at least once, the protecting drug was administered. Following this, vital capacities were again determined and followed by serial administration of the bronchospastic agent at intervals of not less than twenty minutes. Before each successive injection of the bronchospastic agent, three to five vital capacities were always determined at intervals of one to two minutes in order to reaffirm the basal vital capacity from which the amount of drop was to be calculated. The new "basal" vital capacities were sometimes several hundred c.c. higher than the original basal readings; this was due to the previously mentioned rebound phenomenon, to the therapeutic effect of the protecting agent, or perhaps to the bronchodilating effect of repeated forced expirations *per se*. The decrease in vital capacity, when the bronchospastic agent was readministered, was computed from this higher level, which was frequently maintained for a considerable period of time. Consequently, when protection was finally lost, i.e., when the decrease was equal to the control drop, the point to which the vital capacity fell might still be higher than even the original basal determinations. The loss of protection was usually verified by at least one further dose of histamine or mecholy.



The sensitivity of the tracheo-bronchial tree to either of these substances varied in most subjects from day to day. It was minimal during asthma-free intervals and maximal during periods of active bronchospasm. Sensitivity did not usually vary within one day and thus did not affect the course of any one protection study in the vast majority of cases. In a few instances, a small dose of histamine or mecholyl appeared to potentiate the bronchospasm already present, over and above its usual effect. In such cases the vital capacity would fail to rise again over a considerable period of time, or it even would continue to decrease. Studies on subjects in active asthma, on whom an adequate control drop in vital capacity could be obtained, were as satisfactory as studies performed during periods of relative freedom from clinical asthma.

Serial increases in the dose of the bronchospastic agent caused increasing drops in vital capacity which were not always in proportion to the increment in dose. No cumulative effect was noted when the dose that caused a measurable decrease in vital capacity was repeated several times every twenty to thirty minutes. Repetition of the same dose several times during a seven-hour period showed that a refractory state of the tracheo-bronchial tree did not develop during the course of studies carried out for this length of time.

Vital capacity determinations were sometimes invalidated by cough due to the stimulus created by forced expiration or by the bronchospastic agent itself. If this effect was so marked as to preclude accurate, consistent determinations, the test was discontinued. It was possible, however, to carry out adequate protection studies on some subjects in whom a bronchitic element was present. Such patients often experienced a marked decrease in cough after the protecting agent was administered. One protection was established, proper spacing of basal readings, so as not to excite the cough reflex, was no longer necessary. Another interesting observation in such patients was the marked increase in vital capacity and decrease in cough that frequently occurred during the course of obtaining the basal readings. Apparently, the act of forced expiration into the apparatus produced a positive pressure, which was exerted backwards into the tracheo-bronchial tree as an internal distending force. Consequently, the vital capacity often reached a figure much higher than the determinations recorded when the subject first arrived at the laboratory. Care had to be taken that studies were not begun until the vital capacity had been maintained consistently over several recordings.

Data, describing the degree of protection afforded by a given protecting agent against a bronchospastic drug, are derived from these experiments. *We have repeatedly seen that any one protection study in a single individual may have little general applicability.* We have attempted, therefore, to determine an algebraic equation by which the degree of protection could be expressed in terms applicable to many subjects, so that the data might be subjected to some degree of statistical analysis. The decrease in vital capacity produced by a given dose of histamine or of mecholyl varies greatly from individual to individual, but remains constant in the same individual for the period of one protection study. During a period of protection, the decrease in vital capacity produced by the same dose of bronchospastic agent will, by definition, be less than the control drop. We have considered the percentage difference between these two values to be a measure of protection:

$$P = \frac{C - E}{C} \times 100$$

where P is the degree of protection in per cent, 100 per cent indicating absence of any decrease in vital capacity after the administration of histamine or of mecholyl; C is the control drop in vital capacity produced by an injection of the same quantity of the bronchospastic agent before administration of the protecting drug; and E repre-

sents the decrease similarly produced at any given time after the protecting drug has been administered.

Accurate evaluation of protection demands that the control drop in vital capacity exceed 1,000 c.c. We prefer to work within the range of 1,200 to 1,600 c.c. When, for example, 1,200 c.c. is achieved as the control drop, a later decrease of 800 c.c. would appear to indicate a protection of 33 per cent:

$$\frac{1200 - 800}{1200} \times 100 = 33\frac{1}{3}\%$$

However, variations of plus or minus 100 c.c. both in the "basal" vital capacity and in the determination thirty seconds after an intravenous injection of the broncho-

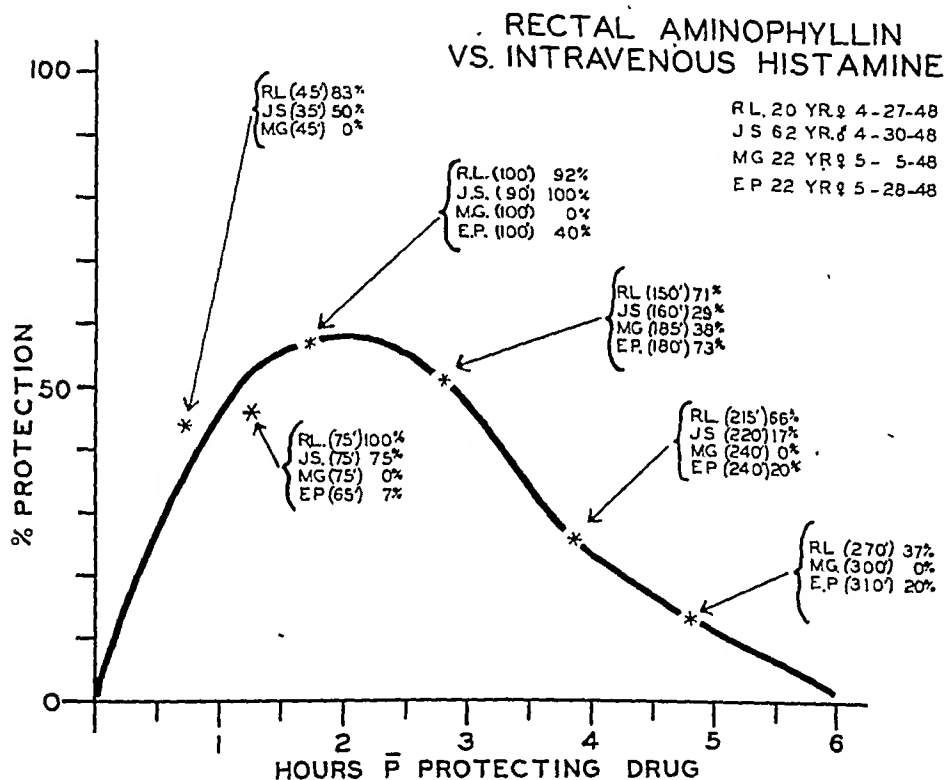


Fig. 3. A typical curve denoting the protecting capacity of a therapeutic substance, in this case aminophyllin given rectally, against the effects of a bronchospastic agent, in this case histamine given by vein. The curve represents the massed data from four protection studies, and thus is derived from a total of thirty individual doses of histamine including the control determinations.

spastic agent may produce, in any individual instance, a total difference of as much as 200 c.c. in the drop. An additional variation of 200 c.c. can be accounted for by virtue of the fact that the bronchospastic agent cannot be relied upon to produce precisely the same effect every time. The total range of variation, then, might be as much as 400 c.c.

If 600 to 800 c.c. is accepted as a control decrease in vital capacity, a later drop (after administration of a protecting drug) of only 200 to 400 c.c. might be considered to demonstrate considerable protection. Obviously, however, this would be open to serious error. Therefore, we have always attempted to attain control drops

## EVALUATION OF THERAPEUTIC SUBSTANCES—LEVINSON ET AL

of 1,200 to 1,600 c.c., and consider protection significant only when it is 40 per cent or more.

This transformation of data from vital capacity readings in cubic centimeters to percentage figures eliminates the dose of the bronchospastic agent from consideration as a variable factor. It also facilitates the statistical presentation of data obtained from experiments on several subjects into one curve of increased statistical probability. Such a graph, representing the massed data from four protection studies, derived from a total of thirty individual doses of a bronchospastic agent, is presented in Figure 3.

### DISCUSSION AND COMMENTS

The results of these studies, with regard to the evaluation of a wide variety of drugs for the treatment of bronchial asthma, are to be reported in detail elsewhere. However, many important lessons have been learned, and much speculative and significant data has evolved in the actual performance of the tests.

The rebound phenomenon is very interesting. This consists of a rise in vital capacity above pre-injection levels after the drop produced by intravenous administration of a bronchospastic agent. This higher level, to which the vital capacity "rebounds," is usually not maintained, but generally settles back to the basal level (Fig. 1). In rare instances, however, the higher level is maintained, so that successive injections of bronchospastic agent, followed by successive "rebounds," have in this manner resulted in a gradually increasing vital capacity without any other form of treatment. This is a possible basis for the recommendations that the acute asthmatic state be treated with repeated minute injections of histamine.

This apparent paradox is not as yet completely explained. Acetylcholine in suitable doses leads to the liberation of epinephrine from the postganglionic cells which constitute the adrenal medulla. One may then postulate that the rebound phenomenon represents the effect of this released epinephrine. In the case of histamine, a somewhat similar argument is possible. It has been felt that the hypotensive effect of histamine is sufficient to excite the pressor receptors of the carotid sinus and aortic arch, leading to the outpouring of stored epinephrine from the adrenal medulla, as well as to compensatory vasoconstriction, and to acceleration of the heart rate. In this connection, it is certain that animals whose adrenals have been removed become more sensitive to histamine shock.<sup>4</sup>

These data should not be considered as supporting the discredited ideas of "desensitization" therapy with histamine. It is to be noted that we are dealing in this case with extremely short-lived experiments from the asthmatic standpoint and that the increment in vital capacity produced is maintained over a period of minutes or of a few hours at most. The deleterious effects of the administration of histamine or of acetylcholine to an individual in an actual attack of clinical asthma undoubtedly far outweigh its possible beneficial effects through this rebound phenomenon.

We have also observed what might be termed a "hyposensitization" to histamine and to mechoyl. Several patients, over the course of months of study, have displayed a decreased reactivity to comparable doses of the bronchospastic agents, particularly to histamine. This was paralleled by general improvement in the state of clinical asthma, yet the same decreased responsiveness was noted even during subsequent brief periods of reactivation of asthma. Hence, the decreased sensitivity to the bronchospastic drug could not possibly be ascribed only to the improved state of clinical bronchospasm. This is to be differentiated from the decreasing sensitivity noted over a short period when protection studies are carried out in a patient during the course of improvement from an acute asthmatic attack.

To what is this decreased sensitivity to be ascribed? Is it a true hyposensitization phenomenon? We are not prepared at this time, on the basis of available evidence, to invoke this mechanism. We feel that the general clinical improvement noted in so

many of our patients is due to many factors. These include constantly maintained reassurance (transference in the psychological sense), improvement in the patient's mental attitude towards his disease, education in therapeutic routines, and frequent breathing exercises and positive pressure applications entailed in the performance of vital capacity determinations over extended periods in the course of protection studies.

It is apparent that there is a difference in the mechanism by which histamine and mecholyl affect the tracheo-bronchial tree. The essential nature of the difference is not clear. Spontaneous observations by many patients disclosed a subjective response more closely paralleling clinical asthma with mecholyl than with histamine injections. Aerosol administration of either substance produces a condition even more closely simulating the clinical asthmatic state.

There has been a not inconsiderable number of patients who failed to develop bronchospasm and decreased vital capacity with fairly large doses of histamine. We have not observed any patient who failed to react to mecholyl at some time. One subject (J.R.), for example, received 0.09 mg. of histamine intravenously without decrease in vital capacity. Another (B.L.) required 0.08 mg. before a decrease in vital capacity of 800 c.c. occurred. Both patients reacted to moderate doses of mecholyl, although the former has subsequently become considerably less sensitive to mecholyl. The insensitivity to histamine may be only apparent in that bronchospasm may have been producible with even larger doses. However, the side-effects of such doses prohibit their use.

An interesting phenomenon has been the variation in histamine sensitivity with phases of the menstrual cycle (subject E.S.). She regularly displayed increased sensitivity just before and during each menstrual period. The obvious inference is that this is in some way explainable on the basis of variations in hormone levels themselves or on one or more of the secondary variations in metabolism paralleling the menstrual cycle.

Even more common have been variations in sensitivity of a seasonal nature. This has been especially apparent in studies performed on patients during and after the pollen season. Several patients so studied were quite sensitive to both histamine and mecholyl during the phase of active asthma. With the end of the pollen season, their sensitivities to both substances decreased markedly. For instance, subject I.D., during the pollen season, showed decreases of 700 c.c. and 1,300 c.c. from a basal vital capacity of 4,000 c.c. after intravenous doses of 0.03 mg. and 0.035 mg. of histamine, respectively. Some weeks later, 0.05 mg. failed to decrease her vital capacity from 4,400 c.c. During the pollen season, her vital capacity was likewise decreased from 4,300 c.c. to 3,000 c.c. with 0.4 mg. of intravenous mecholyl. After the pollen season, 0.4 mg., 0.5 mg. and 0.6 mg. intravenously decreased her vital capacity only 350 c.c., 500 c.c. and 800 c.c., respectively. During a subsequent attack of acute bronchitis, 0.35 mg. intravenously again decreased her vital capacity by 1,300 c.c.

In the above patient, as well as in every other patient studied, aerosols of histamine and mecholyl never failed to cause bronchospasm as evidenced by marked decreases in vital capacity. Subsequent reports will deal with the efficacy of various classes of agents in protecting against the bronchospasm induced by these methods.

#### SUMMARY

1. The history of histamine and acetylcholine derivatives in relation to the allergic state and more specifically to bronchial asthma is reviewed.
2. The evolution of the use of these substances for the induction of dyspnea and bronchospasm in subjects with bronchial asthma is traced.
3. With this technique a method of assay in man of the relative value of new and of accepted therapeutic agents for the relief of bronchial asthma has been

evolved. The development and present status of this technique is the subject of the present report.

4. We have outlined in detail the method of protection studies which we have employed and have devised a formula and method of recording wherein the results obtained may become statistically meaningful and of a general applicability.

5. This method of human assay may enable one to evaluate accurately any new therapeutic agent for the relief of bronchial asthma and further to correlate clinical observations with the physiopathology of the disease.

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# Progress in Allergy

## REACTIONS TO PENICILLIN

### A Review of the Literature, 1943-1948

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This review was written with the hope that it would be considered as a subtraction rather than an addition to the literature on the subject of penicillin sensitivity. It is based on 308 (of nobody knows how many more!) papers published on this topic from March, 1943 to October, 1948, and an additional fifty-two papers, in which sensitivity is mentioned but neither defined nor described. It does not pretend to be complete, since it is still difficult to acquire papers published abroad during the years of the war and known by reference alone to be concerned with penicillin sensitivity.

In cases in which identical, or almost identical, syndromes were reported by a number of different workers, the earliest ascertainable published report was taken for review purposes. No slight was intended to those others, who, for reasons of space alone in both text and bibliography, had to be completely omitted.

It was not planned that all papers on all phases of the subject be mentioned, but only that the welter of unrelated and separately published more important papers concerned with the phenomenon of penicillin sensitivity be brought together in one place, in so far as an orderly arrangement of the subject permitted. Since many of the workers, and especially those earliest in the field, did not, and perhaps could not, differentiate between toxicity and sensitivity, and no exact classification is as yet available, all untoward sequelae to penicillin treatment are loosely, but purposely, termed reactions as noted in the title of the present review.

Although the Floreys<sup>41</sup> paper in 1943 mentioned no evidence of sensitivity in 187 patients treated with penicillin, it quickly became apparent (August, 1943) that untoward reactions occurred:—Keefer and his colleagues<sup>62</sup> reported that of 500 cases, sixty-nine demonstrated reactions as fever in five; chills and fever in twelve; thrombophlebitis at injection site in nineteen; urticaria in fourteen; site-of-injection tenderness in five; headache and facial flushing in ten; testicular tingling in two; and muscular pain in two, due perhaps, at least in part, to impurities in the treatment material. In the next paper published, Lyons<sup>75</sup> reported urticaria as the commonest single complication as occurring in 5.7 per cent of 209 surgical (U.S. Army) cases. The author was able to classify the patients into two broad groups: those who had reacted to a particular batch of penicillin with chills, headache, facial flushing, muscular cramps, nausea, vomiting and eosinophilia and those who reacted to any type of penicillin with fever, urticaria and transient azotemia.

By 1946, Duemling<sup>32</sup> was able to summarize the results of therapy in 17,879 Naval patients treated with penicillin for sixty-five clinical conditions. Of these, 892 presented latent, early and neurosyphilis. Of the total group, 10 per cent are listed as having suffered Herxheimer reactions, urticaria, pruritus and fever.

In 1948, Thomas and his colleagues<sup>126</sup> were able to list the reactions in order of decreasing frequency as seen in 10,000 syphilitic patients. Urticaria, which was most common, occurred seven to twelve days after the beginning of treatment in approximately 2.5 per cent of the cases and lasted four to five days, irrespective of the continuance or discontinuance of penicillin therapy. Of 804 patients treated for eight days with penicillin oil-beeswax, two developed angioneurotic edema on the seventh day, but in the majority of cases the penicillin therapy could be continued for eighteen to nineteen days. In three cases, severe urticaria and angioneurotic edema necessitating discontinuation of treatment occurred on the eighth or ninth day, but treatment was resumed ten days later without recurrences. Exacerbation of secondary syphilitic lesions took place six to ten days after treatment started and resembled a relapse excepting that dark field examinations were negative. Erythematous, or papular, eruptions were seen in twenty-five patients within the first forty-eight hours after treatment was initiated and lasted one to three days, all cases continuing their penicillin therapy. Localized dermatitis was seen in very few patients and developed three to four days after treatment was started. A bullous dermatitis

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occurred in two patients, seven to ten days after treatment was initiated and it was necessary to discontinue treatment in one patient, but it was possible to resume treatment after ten days without untoward reactions. The same patient had three recurrences with generalized urticarial eruptions and bullae two months following his discharge from the hospital.

In the series by Cornia *et al*,<sup>23</sup> reactions were seen in 0.5 per cent of 2,000 soldiers given prolonged penicillin therapy; these included urticaria, complicated by angio-neurotic edema, shock and convulsions or psychotic depression, a syndrome resembling serum sickness, acute syncope with transient miliaria-like eruptions, erythematous vesicular eruptions, dermatophytid-like eruptions, erythema nodosum, and epididymitis. In this group of patients, intradermal tests with three brands of penicillin showed that reactions occurred in 84 per cent to one brand and 65 per cent and 23 per cent respectively to the other two. Some patients with severe penicillin sensitivity gave negative tests and some positive reactions occurred in the 116 control subjects. Crystalline penicillin also caused skin reactions.

In the series of 124 male patients studied by Kolodny and Denhoff,<sup>20</sup> 16 per cent showed immediate reactions and 7 per cent delayed reactions, both occurring together in some individuals. The immediate reactions affected 25 per cent of the dermatological but only 6 per cent of the general medical and neurosyphilitic group. Of twenty-one patients with skin diseases, all showed exacerbations of the existing lesions. In some cases, it was associated with a generalized rash, periorbital or labial edema, gastrointestinal symptoms and an "id" reaction. The greater number of reactions appeared within twenty-four, and subsided within ninety-six hours. The incidence of delayed reactions was approximately the same in both the dermatological and the other groups, the symptoms beginning in all but one case in seven to fourteen days and subsiding in four to five; all the patients showing generalized urticaria with pruritus, but some presenting, in addition, swelling of the joints, facial edema, moderate lymphadenopathy, generalized arthralgia, myalgia and malaise. In twelve patients, reactions were produced consistently only if a week or more had elapsed between courses of treatment, suggesting an anergic state of sensitivity. Skin tests done with solutions of 1000 or 2000 U/c.c. (0.1 c.c.) produced consistent reactions, eleven of fifteen reactors, however, giving positive responses to trychophyton skin tests, whereas only two of fourteen non-reactors were positive to penicillin. The conjunctival tests with penicillin were uniformly negative for this group.

In a series of 618 patients studied by Hopkins and Lawrence,<sup>57</sup> seventy were given penicillin by oral and/or intramuscular administration, 492 locally and fifty-six both locally and systemically. Reactions occurred in sixty-five (11 per cent): in one as a generalized urticaria, in three others during an attempt at desensitization and in seven more during tests. Three patients experienced severe pruritus after intramuscular injection, but in only one case was this sufficient to require hospitalization. In eight patients there was a disseminated erythematous or vesicular eruption and in fifty-six a localized dermatitis seen most frequently in those with a pre-existent eczematous dermatitis. Herxheimer reactions were seen in three and local gluteal reactions in two. Tests demonstrated that a sensitization occurred in 13 per cent of the cases treated with ointment; and in 21 per cent of the patients presenting eczematoid lesions. Patch tests were done with penicillin ointment (100,000 U/gm) intradermal tests with penicillin saline solutions (10,000 U/c.c.), and passive transfer tests were done with the patient's serum and saline solutions (100,000 U/c.c.).

Of nineteen patients who gave positive intradermal reactions to 1,000 units of commercial penicillin, thirteen were positive to the same amount of crystalline penicillin G. Of ninety patients tested, twenty-three gave positive reactions to 100,000 units of penicillin injected intramuscularly, responding with urticaria, erythema and intense generalized pruritus and dermatitis. Of 405 patients given intradermal and patch tests, fifty were positive and 335 negative to both tests, whereas six were positive to patch tests only, and fourteen to intradermal tests only. The authors conclude that sensitization sufficient to prohibit future penicillin therapy would probably occur in less than 1 per cent of the patients treated. They also state that the response to skin tests may vary from week to week and, if possible, may actually become negative.

The reactions to penicillin appear also to depend upon the method of administration. Kern<sup>65</sup> in his case report described a thirty-eight-year-old woman, for whom oral penicillin was prescribed in 10 drops of the 100,000 U/5 c.c. saline solution placed on the tongue every two hours. By the second day, the patient had complained of burning and stinging and presented a sore tongue and throat with tender gums. There was infection of the soft and hard palates, the oral pharynx, the tongue and the gums, with fissuring of the tongue. Symptoms disappeared after three days.

In a similar report, Goldman<sup>47</sup> described a female patient of sixty-one with a recurrent aphthous stomatitis of 15 years' duration. Calcium penicillin ointment was applied three to four times daily with rapid improvement, excepting for one large linear ulcer below the gum. Application of the ointment to this lesion was difficult and a mouth wash of 500 U (sodium penicillin)/c.c. in saline was substituted. Within two days the patient presented a vesicular cheilitis with considerable edema. Patch tests with calcium penicillin ointment were negative, but a positive reaction was seen to the sodium penicillin solution used, although three other brands of sodium penicillin produced no reaction. Application of the reacting solution to the lips produced an edema within twenty-four hours, demonstrating a specific sensitivity to a saline solution of a specific brand of sodium penicillin.

The specificity of the reaction is demonstrated by Wright and Rule<sup>42</sup> who reported severe reactions in 16 per cent of thirty-eight patients treated with penicillin calcium lozenges. The patients demonstrated sore throats, extreme dryness and a burning sensation in the mouth and lips, impaired taste, sensitivity to hot foods and drinks and salty and spiced foods. In three patients a stomatitis developed and persisted for one or two weeks, being followed by a transient exfoliative type of lesion. The discomfort increased for one to two days following discontinuance of therapy and then gradually decreased. The mild glossitis and a sense of dryness persisted in some patients for several weeks. Lozenges of penicillin sodium caused reactions in 9 per cent of 151 patients, proving sensitivity present to both types of penicillin. In the report of the Permanente Foundation<sup>48</sup> seventeen instances of glossitis and stomatitis due to penicillin lozenges were listed, the incidence of reactions with calcium penicillin being given as 18 per cent. The lozenge ingredients were calcium penicillin, powdered sugar and calcium stearate. The binding agent, if any, is not given.

In Kleinfeld's<sup>66</sup> report of six patients given oral and mucous membrane topical applications there was acute rhinitis, stomatitis and glossitis following instillation of penicillin nose drops and oral pastilles in one patient whose glossitis was aggravated after administration of the nebulized penicillin solution. Two additional patients developed lesions of the mouth following the oral penicillin and one a dermatitis of the nares after application of penicillin ointment. In two patients there were abdominal cramps and distention following the ingestion of three enteric-coated tablets and tablets buffered with sodium citrate, respectively, each containing 250,000 units of penicillin. All cleared when the penicillin was discontinued.

Early in 1946 there was correspondence in the British medical journals concerning local oral penicillin reactions. Bedford<sup>5</sup> described melanoglossia (black tongue) in two patients using penicillin lozenges or penicillin throat sprays. The condition occurred on the second post-treatment day in one patient, whose tongue presented a black velvety coat which disappeared on the eleventh day, the tongue becoming normal seven days later. In a second patient, a black tongue developed on the second and became normal on the sixteenth post-treatment day. The author suggested that the "mycotic black tongue may have resulted from an alteration of the normal biological balance of the mouth by the penicillin." Ellinger and Shattock<sup>35</sup> called attention to two of their patients with black tongue following the oral administration of both sulfadiazine and penicillin. The patients treated with penicillin showed, in addition, symptoms of nicotinamide deficiency with skin changes, abdominal pain and sensory disturbance. The level of nicotinamide in the urine indicated deficiency and the symptoms were reproduced by a second and third course of oral penicillin. The patients' symptoms were relieved rapidly by the administration of 100 mg. of nicotinic acid. Thompson<sup>127</sup> noted soon that irritation did not occur in thirty patients given troches with a gelatin base. Further correspondence by MacGregor<sup>78</sup> and by Kerfoot<sup>64</sup> suggested discoloration as due to the base, since the former reported on 1,000 patients treated with gelatin pastilles with only occasional tongue discoloration and no stomatitis. The latter showed that no instances of stomatitis occurred in the patients using the lozenges made with the sucrose base prepared and dried by compression. That these factors are not the complete story is seen by the letter from Mutch<sup>91</sup> who again reports the occurrence of black tongue following oral inhalation and nebulized aqueous solutions of high potency yellow penicillin in a patient taking 50 mg. of nicotinic acid daily. Mutch concludes that the reaction is not due to avitaminosis caused by penicillin inhibition of the nicotinic acid producing bacteria of the gut, but to a local reaction of penicillin itself. Dr. Harold A. Abramson and the present author were able to show that glycerite of hydrogen peroxide in the 1:3 or 1:4 dilution of the 2.5 per cent solution completely cleared this condition.

Penicillin by mouth does, however, cause local reactions as seen by the report of Marcovicci<sup>51</sup> who described six cases, the mildest being an aphthous stomatitis.

In the remaining patients there was a parasitic stomatitis (thrush) which developed during the course of penicillin therapy for infectious mononucleosis; two cases of virus pneumonia and one of streptococcus sore throat. In Brown's case report<sup>12</sup> the patient presented a glossodynia and exfoliation of the filaments of the filiform papillae of the tongue which appeared on the second day following the use of 10,000 U/c.c. penicillin solution as a throat swab and gargle, the papillae of the tongue becoming yellowish brown and felt lifeless. On the third and fourth days the tongue was tender, red and swollen and the filaments easily rubbed off. The tongue became normal in appearance three to four days following treatment with hot saline gargles and the filaments regenerated in two to three weeks.

Cook<sup>20</sup> subsequently reported on twenty-eight patients in four of whom oral penicillin preparations caused stomatitis and glossitis, occurring in one patient 1½ days after using penicillin troches. By the fourth day there were great blisters on the tongue, the soreness disappearing in about a week and the blisters persisting for about a month. A patch test with a portion of one of the troches elicited a wheal and flare in forty-eight hours. Segal and Ryder<sup>110</sup> had previously reported that of the sodium and calcium salts used for inhalation, the latter was the less irritating, although in some patients edema of the lips or oral mucosa and generalized urticaria appeared, the former being controlled by changing the brand of penicillin and the latter by oral administration of Benadryl. Irritation of the tongue and oropharynx was minimized by changing to other lots of penicillin. The sore tongue and oral stomatitis was treated by saline rinses, by dental hygiene and by frequent sips of water during the treatment period.

That the reaction may not be necessarily local is shown by Wheatley's report<sup>130</sup> of a patient in whom a chickenpox-like rash appeared on the face and chest 20 minutes after the use of a penicillin lozenge, the rash being accompanied by a hot, tingling sensation of the skin and fading in 20 minutes. On the other hand, in the report by Oberst and Murray<sup>93</sup> a severe dermatitis occurred in one of the authors after a large oral dose of penicillin had been taken while he was serving as a subject for the urinary excretion and blood-level studies being done. The patient had previously suffered a reaction following the intravenous administration of 50,000 U. of penicillin, the dermatitis appearing within an hour and being followed in several hours by reddening of the face and itching of the scalp and toes, with areas of erythema over the chest and swelling and blisters around the toes. Subsequently, the same dose was given orally on about 10 occasions, without producing a reaction, but when a dose of 500,000 U. was given by mouth a severe dermatitis occurred, followed in about two hours by itchiness and swelling and blisters of the toes and swelling and reddening of the eyes. There was no previous history of eczema or allergic reactions and the penicillin used was suspended in oil and beeswax enclosed in a gelatin capsule. Since the oral dose, which produced the reaction, was 10 times the intravenous dose, it appears that the penicillin concentration of the blood and tissues was probably about the same in both instances.

In an individual case report, Scott<sup>100</sup> described the occurrence of edematous lips and large urticarial wheals on the abdomen, thighs and upper arms of a four-and-one-half-year-old boy who was sucking penicillin lozenges for the treatment of an enlarged and discharging tonsil. A positive reaction was obtained to a patch test with penicillin ointment (500 U/Gm). The patient's father developed hydroarthrosis of the joints of the knees and fingers while using penicillin lozenges, the joints becoming normal twenty-four hours after the penicillin was discontinued. He also presented a positive skin test.

During the first years in which penicillin was used, it was considered that prolonged contact caused the local reactions. Pyle and Rattner<sup>102</sup> reported early in 1944 that a medical officer in charge of preparing the penicillin solutions, as well as administering the drug to patients, presented an eruption which began as a mild marginal blepharitis and conjunctivitis which spread to the bridge of the nose and far into the central oval of the face, resembling an acute dermatitis due to contact with an irritant. Within a few weeks eczematous lesions appeared on the hands and penis, the eruption completely disappearing in two weeks following his cessation of handling penicillin. In this patient, a patch test to penicillin elicited a strongly positive reaction, additional patch tests indicating that it was the penicillin, not the medium in which it was cultivated, which was responsible for the contact dermatitis. Silvers<sup>115</sup> reported on a chemist who worked for one year with penicillin before developing an itching rash of the eyelids and penis. The patient gave a positive patch test to the yellow amorphous form of penicillin sodium, but a negative test to the pure crystalline sodium penicillin. The rash disappeared entirely when direct contact with penicillin was avoided.

Binkley and Brockmole<sup>5</sup> treated two physicians who were engaged in administering

penicillin to hospital patients, their dermatitis developing within a few weeks after the first use of the drug. Patch tests with a solution of penicillin sodium containing 5,000 U/c.c. was strongly positive in one, whose eruption covered the forehead and lower arms. The patch tests were negative in the second, although an intramuscular injection of (0.000 U' caused pruritus and an eruption of the hands and feet. The dermatitis of both men disappeared when contact with the drug was avoided or minimized.

Barker's<sup>54</sup> patient was a medical officer in charge of a penicillin laboratory of a large hospital. He had handled penicillin under laboratory conditions for seven months with no untoward effects, but one day while dispensing penicillin solutions, spilled some on his hands. The next day there was a pruritus of the face, which disappeared while he was on leave. As soon as he returned, however, to dispensing the penicillin solutions, an acute dermatitis of the face and neck developed with an edema of the upper and lower eyelids and a tightness of the skin of the face, followed by a vesiculation and serous exudate of the chin. Patch tests made with penicillin solutions (20,000 U/c.c.) produced an eczematous reaction in twelve hours, but the same solutions, after autoclaving, were negative. The authors suggest that in this case the irritant in the penicillin solutions might be volatile, due to the selection of the face as the first site of attack and the disappearance of the effect with autoclaved solutions.

The great variation in the type of contact reaction was demonstrated by the patients reported by Catherine MacLinnie<sup>55</sup> whose patient, a nurse, had reacted with generalized urticaria following the therapeutic administration of penicillin. Two months later a generalized itching and wheals on the legs occurred forty-eight hours after handling the drug and entering a room where penicillin was being prepared produced a nasal congestion. A second patient, who had never received penicillin therapeutically, but had been handling the drug intermittently over a period of several months developed an itching, redness, whealing and a fine papular rash of the face and arms associated with photophobia and nasal congestion when contact with the drug became more frequent.

The amount of contact dermatitis due to penicillin was indirectly ascertained from the patients who used an ointment containing the drug. In the cases described by Cohen and Pfaff,<sup>56</sup> 4 per cent of 100 patients presented contact reactions following the use of an unguent containing 50,000 U/oz., in 50 per cent hydrous wool fat and 50 per cent rose water.

The patient may be sensitized at one site and react generally as shown by the report of Michie and Baillie,<sup>57</sup> whose patient had penicillin sodium solution instilled into a wound on September twenty-four and undiluted penicillin powder applied to a sinus on October 2, the wound having completely epithelialized by October 10, when two drops of penicillin solution (100,000 U/c.c.) were instilled into the ears for a mild chronic bilateral otitis externa, both the ears and the almost-healed leg wound beginning to weep copiously. A patch test made on the arm with the penicillin solution used produced a weeping eczema similar to the affected area, the eczematous weeping eruption spreading to the face.

According to Morginson,<sup>58</sup> who treated 102 dermatological conditions in eighty-five patients, topical applications for longer than three to four days frequently induces contact dermatitis. In some cases, however, as seen in the patient described by Markson,<sup>52</sup> penicillin ointment applied in the case of mild conjunctivitis caused an edema of the eyelids by the next morning and when the ointment was re-applied after discontinuance for one day the edema became more pronounced and was associated with an erythematovesicular dermatitis appearing on the eyelids and other parts of the face. The patient had previously been treated with sulfathiazole ointment, for which the patch test was negative, although a test to the penicillin ointment produced an erythematovesicular eruption. The ointment base was the same for both preparations.

The patient described by Bedford<sup>6</sup> was evidently sensitized by mouth and responded by contact. Having been successfully treated for a nasopharyngitis and tracheitis with penicillin pastilles (300 U) and a throat spray (250 U/c.c.) he responded one week later when penicillin solution (250 U/c.c.) was instilled hourly for a mild conjunctivitis with an itching vesiculopapular rash which appeared on the lower lids where the excess solution had been wiped away. The rash subsided in 8 days. Of interest is the fact that the patch test made on the arm with the original solution, which had been allowed to become inert, as well as with a fresh penicillin solution, gave negative results. A fresh solution, however, gave a positive reaction when used as a test on the site of the previous lesion.

In some patients such sensitivity may be of more than one type. Benkwith<sup>7</sup> treated a Naval officer for a diffuse palpebral conjunctivitis with penicillin calcium solution,

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instilled in the lower conjunctival cul-de-sac hourly for two days. A typical allergic dermatitis appeared on the eyelids, nose and adjacent face. A patch test using the ointment produced a very severe reaction, the base being negative. An intradermal test with the penicillin solution used produced an urticarial wheal, the patient being equally allergic to penicillin from two different manufacturers.

The length of time necessary for the development of sensitization may vary greatly, as seen in the case described by Vickers<sup>130</sup> whose patient had penicillin powder applied to abrasions on the leg at various times from May 22 to July 5, 1945, and was then treated by intramuscular penicillin drip until July 12. At this time a dermatitis appeared at the site of the drip and a penicillin spray was used locally, resulting in erythema, vesiculation, weeping and crust formation over the inner surface of the leg. Patch tests with the penicillin solutions used were strongly positive in twenty-four hours. The incubation period for this sensitivity was evidently approximately forty days.

Few patients present the variegated sensitivities to intense study and treatment as that described by O'Donovan and Klorfajn.<sup>94</sup> In June, 1944, the patient presented fissures of the left foot treated with penicillin sprays without benefit. In October, 1944, an abscess of the left jaw was treated for three days with penicillin sprays. Two weeks later a rash developed, both on the left foot and on the face. This subsided, but in December a recurrence of the foot condition was treated with a penicillin spray, resulting in a rash at the site of the spray and on the face. The patient gave positive patch tests, intradermal tests and spray tests with the penicillin solution. An intramuscular injection of 15,000 units of penicillin produced severe anaphylactic shock, followed in six hours by swelling, reddening and oozing of the face, and redness and weeping of the right eye. Exposure to ultraviolet light, both by sun and lamp, produced erythematous reactions. An attempt to desensitize the patient by the subcutaneous injection of 100 units of penicillin produced a mild shock. Penicillin (15,000 U.) capsules given orally caused swelling of the face, neck, scalp and ears, a leukocyte count of 16,000, and complaints of malaise and drowsiness. The oral treatment was continued for thirty days, following which the patient became negative to patch tests and no longer presented the actinic reaction. In this patient, regardless of the means by which penicillin was administered, the skin reactions occurred only at the sites initially treated, demonstrating a purely local sensitivity.

Templeton and his colleagues<sup>125</sup> reviewed the toxic reactions occurring after the topical application of penicillin solutions and ointments, after the injections and after oral administration. They recommended that topical use be avoided. Their studies show that the application of a 1,000-unit penicillin solution to the skin of seven subjects at the site of a previous injection of the serum of patients who reacted to penicillin caused positive reactions.

The medium in which the penicillin is dissolved must, however, not be completely ignored, since in Meara's report<sup>131</sup> patch testing of three patients with skin sensitivity to penicillin revealed that the penicillin as such was not responsible for the eruptions. The incorporation of the penicillin in a non-offensive cream base was necessary before sensitization took place in one patient. In two other patients, an ingredient of the ordinary ointment base was the responsible agent.

The exquisite sensitivity which may develop with contact to penicillin is shown in the report by Prince,<sup>101</sup> whose patient showed an eczematous reaction to contact with penicillin, an injection of 0.02 c.c. of a 1 unit/c.c. strength causing an eczematoid eruption on distant parts of the body, with sneezing as well as local itching from the injections.

Studies to elicit the cause of such cutaneous reactions have been done by Goldnan and his colleagues.<sup>45</sup> In 350 cases of various cutaneous conditions treated with topical penicillin, sixteen responded with an eczematous reaction. All but two gave positive patch tests, the patients being tested with impure commercial penicillin, crystalline penicillin and penicillin inactive (according to assay), or inactivated by penicillinase. Of thirty-two men with acute pyogenic infections, nine developed contact dermatitis following the use of the ointment, although only three of eight women with similar lesions reacted in this way. Patch tests on 216 control patients, with an ointment containing 18,000 U./cm. of commercial calcium penicillin produced no reactions during an observation period up to seven days. When retested two weeks later, however, thirty-five of the patients reacted positively. It was determined that penicillin ointment in the concentration of 18,000 U./gm. was not a primary irritant. In this series, seven cases of patients with urticaria following the parenteral use of penicillin gave negative skin and passive transfer tests.

Friedlaender *et al.*<sup>132</sup> carefully studied four of five patients presenting contact

dermatitis resulting from the handling of penicillin. Patch tests were made with all of the substances entering into the manufacture of penicillin by the submerged broth method. Tests were also done intradermally with mould extracts. Three patients gave positive reactions to crystalline penicillin as well as to various intermediate products. One patient gave a positive reaction to *Penicillium* mould; one patient reacted strongly to chloroform extract, and one gave a mild reaction to the mould mycelium. None reacted to the corn steep liquor. Contact periods of nine to eighteen months were required before sensitivity developed.

Since urticaria seems to be the most common reaction, its varieties merit detailed description. Hives may appear in a period as short as twenty-five minutes and up to and beyond the thirty-fifth post-treatment day. Strickland's report<sup>121</sup> concerns a twenty-two-year-old male, who ten weeks previously had received successful penicillin treatment for a gonococcal urethritis and who, when given an intramuscular injection of 20,000 units of penicillin for cellulitis in the perineal region, developed a generalized urticaria with a bilateral periorbital edema associated with pain and effusion of the right wrist joint and edema of the pharynx and larynx characterized by hoarseness and difficulty in swallowing within twenty-five minutes after the initial injection of the second course of treatment. Epinephrine (0.5 c.c. 1:1000 solution) was administered and within twenty-four hours the condition completely cleared. In Krauel's case<sup>70</sup> 10,000 units of penicillin sodium caused urticarial pruritus, redness and intense itching of the palms of the hands in a seaman, who two days later presented pain in the right knee and the left ankle with a temperature rise each evening. This patient had a history of hay fever while cutting grain infested with the rust fungus and of sensitivity to house dust.

In the case described by O'Donovan and Klorfajn,<sup>24</sup> the local reaction occurred six hours after injection. The patient's initial contact had caused no difficulties, while four months later, three days of penicillin treatment was given without untoward reaction. Two weeks later the application of penicillin by spray caused an immediate response with edema of the upper lip, nose and eyebrows and a maculopapular rash of the cheeks and neck. An intramuscular injection of 15,000 units of penicillin caused anaphylactic shock within fifteen minutes, with a local reaction occurring on the face six hours after injection. Three weeks later exposure to ultraviolet light caused a repetition of the reaction in the patient who by now showed positive patch, intradermal, and intramuscular sensitivities. Canizares<sup>26</sup> had the year before questioned whether penicillin was a photosensitizing agent, since his patient, who was treated with 10,000 U. penicillin every three hours to total 50,000 units, had (when taking a sun bath the following day) developed a severe sunburn, which subsided. A morbilliform eruption appeared on the previously sunburned areas four days after the penicillin treatment and faded after two days.

Cuthbert's case<sup>26</sup> developed hives one day after the cessation of penicillin therapy during the course of which the patient received 6,400,000 units in sixteen days following Caesarean section. The hives lasted 6 days and were accompanied by severe pruritus but not by fever or tachycardia. In the case studied by Flinn *et al*<sup>40</sup> the patient had six months previously received 4,000,000 units of penicillin intramuscularly. She developed a pruritus and a severe urticaria with a rise in temperature after being given 200,000 U. of Brand B penicillin intravenously daily for nine days and 30,000 at three-hour intervals intramuscularly for another two days for treatment of a respiratory tract infection. The severe urticaria and pruritus subsided seventy-two hours after penicillin withdrawal. In this patient, intradermal tests showed sensitivity to Brands A, B, and C but not to D. The treatment was continued with this latter brand with no reactions. Six weeks later the patient had lost her sensitivity to Brand B, which could be used for treatment. The authors believe that the incidence of urticaria in penicillin-treated patients is approximately 3 per cent.

In four patients studied by Macev and Hays,<sup>76</sup> the allergic manifestations appeared two to five days after penicillin was discontinued, the patients presenting an increase in pulse rate and elevation in temperature, a swelling of the face and hands, with elevated erythematous lesions accompanied by intense itching. Symptomatic relief was achieved with the administration of 10 per cent calcium gluconate or 50 per cent dextrose given intravenously. Each of the two cases described by Watson<sup>137</sup> is interesting; the first because the patient responded by drowsiness and indigestion as well as urticaria persisting for seven days after receiving penicillin 250,000 U. in distilled water b.i.d. for three days. The symptoms persisted for seven days in spite of the administration of Benadryl and epinephrine. The second patient, previously having been successfully treated for a carbuncle with 150,000 U. of penicillin in distilled water every three hours for five days received gluteal injections of 250,000 U. of penicillin beeswax in oil b.i.d. twice daily for three days for a second carbuncle. Eight days after the first injection, itching and a wheal at the site of an



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old bee sting developed with urticaria and swelling of the sites of injection persisting for one week. Exacerbation of symptoms occurred when the patient ate honey. Benadryl controlled the allergic reaction but only to a slight extent.

The patient described by Price<sup>100</sup> was given intramuscular penicillin, 20,000 U., three hourly and on the fifth day of treatment developed a punctate purpuric eruption on the arms, abdomen, chest and back. On the same day, a small urticarial wheal appeared on the left upper arm and two days later there was a severe giant urticaria with a rise in temperature, a periarticular arthralgia and increase in white count to 17,700 with the appearance of pus cells and casts in the urine. The reaction responded to epinephrine therapy. Scratch and patch tests with penicillin solutions were negative, although an intracutaneous test of "human serum containing penicillin" produced a positive reaction.

In Tripoli's case report<sup>128</sup> one patient developed urticaria and fever on the fourth day and the second a temperature of 101°-103° F. on the seventh day. Wilensky's<sup>141</sup> patient, given penicillin 30,000 U. four hourly for five days presented an elevated temperature of 104° F. with the appearance of a scarlatiniform rash covering the trunk, abdomen and thighs. By the sixth day the condition had become more severe, spreading to the thorax, neck, face and arms, the patient dying of fatal delayed anaphylactic shock on the eighth day.

Although in a number of individuals the onset of urticaria is seen in those who are taking a second course of penicillin therapy, some patients develop a sensitivity after the third course, as noted in the report by Dolan,<sup>30</sup> whose patient had received penicillin intramuscularly two months and one year previously. He developed a severe angioneurotic edema and muscle pain six days after taking 200,000 U. of penicillin orally for a head cold and a mild otitis media. The urticarial reaction was associated with itching. The muscular pain was controlled for six days by Benadryl but still present in some degree one month after cessation of treatment.

That both an acute early and delayed reaction to penicillin may occur is seen by the report of Burt and Caplan,<sup>13</sup> whose patient was given penicillin oil and beeswax for the treatment of a furuncle. Six hours following the initial injection which was made in the midportion of the left thigh the area down to the knee was sensitive and three hours later motion was not possible. There was a concomitant fever, headache and malaise. The following day the area appeared normal but there was a serous exudate of the knee joint and weight-bearing was painful. Since the furuncle was still firmly inflamed, crystalline sodium penicillin G in aqueous solution was given intramuscularly in the right buttock, as two injections of 100,000 U. on successive days. The symptoms of the previous reactions subsided and the furuncle healed, but nine days after the initial injection there was a pruritic urticaria of the area and the exudate from the knee joint reappeared, followed two days later by swelling of the left thigh, the leg and the ankle, the skin being thickened and doughy. The pruritus was controlled by PBZ, the other symptoms subsiding in four days. The patient had a history of ragweed pollen sensitivity and the authors suggest that the reaction may have been due to ragweed pollen and the beeswax or to an early serum-sickness-like reaction to penicillin.

A severe urticaria occurred in 11 days after intramuscularly administered penicillin was reported by Walley,<sup>126</sup> whose patient, a thirty-two-year-old Army officer, received five injections of sodium penicillin twelve hourly for the treatment of an infected hematoma. In eleven days after treatment was discontinued, the patient presented a widespread urticaria with intense pruritus, associated with fever, anorexia, indigestion and vomiting. The patient was unable to tolerate Benadryl. The symptoms subsided slowly during the following eight days.

Urticaria occurring in a physician thirteen days after the cessation of penicillin therapy is described by Strazza,<sup>129</sup> whose patient was given 20,000 U. intramuscularly, three hourly, for a total of 500,000 U., with itching of the site of injection and flushing of the face during therapy. The patient returned thirteen days later with an urticaria and pruritus so severe that he required 6 cc of epinephrine (1:1000), the urticaria covering the buttocks, back, face, hands, feet and uvula, and increasing within thirty hours to so great a degree that the patient had difficulty in swallowing due to edema of the pharynx and uvula. Within forty hours there was stiffness of the neck, the symptoms subsiding in three days. A scratch test to the penicillin used was negative.

In Truitt's<sup>129</sup> patient a painful arthritis, angioneurotic edema and generalized urticaria developed fourteen days after treatment with penicillin had stopped. In this case, patch, intradermal and passive transfer tests were all positive, the first two being still positive nine months after the reaction. A patch test remained positive four months after the reaction but passive transfer tests were negative.

The interval between courses of treatment may be important as shown in the case

described by Criepe<sup>27</sup> whose patient, a twenty-three-year-old male, had received 200,000 U. of penicillin daily for fourteen days. On resumption of therapy after a ten-day interval, the first injection caused a severe generalized urticaria, which persisted for six days, during which time 120,000 U. were nevertheless administered daily. Although direct skin tests with penicillium extract were negative and the presence of anaphylactic antibodies could not be demonstrated in the patient, serum direct intradermal skin tests, passive transfer tests and precipitin tests were positive to the penicillin drug solution used.

Shawyer's<sup>114</sup> case report is concerned with a thirty-four-year-old physician who received 7,500,000 U. of penicillin five days for a bone abscess. His condition improved until seventeen days after discontinuance of penicillin, when a general simple urticaria, uncontrolled by Benadryl, appeared. By the second day the patient developed an angioneurotic edema and by the fifth, a generalized swelling of the joints with intermittent edema of the fauces, glottis and tongue, bronchial asthma and paroxysmal rhinorrhea. The urticaria and the joint lesions subsided following a course of synthetic Vitamin K. The patient did not respond to Benadryl, epinephrine or Anthisan. Vitamin K, however, in 20 mg doses, caused immediate disappearance of the pruritus.

Severe urticaria occurring twenty-one days after the termination of a four-day course of penicillin treatment is reported by Mandel et al.,<sup>50</sup> whose patient, an eight-and-one-half-year-old child, was given penicillin because of a secondary rise in temperature and earache during the course of an acute upper respiratory tract infection, the dose being 0.5 c.c. of calcium penicillin in beeswax and peanut oil by intragluteal injection once daily for three days. The patient also received 100,000 U. orally for one day. Swelling, induration and erythema developed at the sites of injection, being most prominent on the fifth and seventh days after discontinuance of therapy. These subsided with local treatment, but twenty-one days later the patient presented a swelling of the cervical lymph nodes and fever (102.5° F. rectally) followed in twenty-four hours by urticaria, angioneurotic edema, anorexia, vomiting and general malaise. The symptoms subsided in seven days, but fourteen days later (forty-four days after discontinuance of penicillin) giant urticaria and angioneurotic edema developed, subsiding in four days, the residual exfoliation and pruritus persisting for about one month. Scratch tests with calcium penicillin-beeswax-peanut oil, its constituents, the amorphous sodium penicillin and crystalline potassium penicillin, as well as trychophytin tests, were all negative, excepting for a moderate erythema at the scratch test sites of penicillin in oil-beeswax.

Hinman et al.<sup>5</sup> described delayed reactions in seven patients, occurring two to twenty-eight days after cessation of therapy, the symptoms being giant urticaria, intense pruritus, scarlatiniform eruptions, severe arthralgia, hydroarthrosis, ecchymoses and subcutaneous nodules as well as systemic manifestations including fever, prostration, gastrointestinal symptoms, severe headache, mild leukocytosis and albuminuria. The incapacitation lasted about two weeks. In their patients the reactions were not related to the size of the dose, the duration of therapy, the route of administration, previous penicillin therapy or a history of allergic conditions, such as asthma, hay fever, or urticaria.

A generalized urticaria and angioneurotic edema appeared five weeks after parenteral administration of 100,000 U. for five days in a patient described by Scott, Murray and Turnbull.<sup>109</sup>

Urticaria may also be due to concomitant treatment as seen in the patient studied by Grolnick and Loewe.<sup>11</sup> Receiving combined treatment with penicillin and heparin daily, he developed a reaction comprising chills and fever on the sixteenth day when a total of 1,600 mg. of heparin had been given. The therapy was resumed 12 days later and continued for twenty-eight days. The subcutaneous injection of heparin concomitant with the intramuscular injection of penicillin for three alternate days after a two-day rest resulted in another reaction. Further attempts to administer the drugs produced erythema and urticaria in addition to the chills and fever. Reagins were present to heparin, beef serum and beef lung. The heparin rather than the penicillin was considered the cause of the reaction.

Although urticaria may be the sole reaction to penicillin, it may occasionally be associated with other signs and symptoms of serum sickness. Sullens<sup>122</sup> presents a case history which illustrates the difficulty in determining the causative agent of the allergic reaction to the therapeutic use of the antibiotic agent. A white seaman, who complained of a purulent urethral discharge and dysuria occurring six days after sexual exposure, was given sulfathiazole for three days with no improvement. He was then given 100,000 U. of calcium penicillin in five intramuscular injections at three-hour intervals, which resulted in freedom from symptoms within one day and a negative prostatic smear two days later. The patient returned in three weeks with



the recurrence of his urethral discharge and a second course of 100,000 U. was given, the patient being well for six days, at which time he developed large urticarial welts on the abdomen, back, hips, with arthralgia of the wrists and ankles and an edema of the hands and feet associated with a generalized lymphadenopathy, headache and a temperature of 99°F. The condition remained unchanged for three days, the urticaria spreading, however, to the extremities, face and scalp, the wheals measuring 2 x 15 cm. Although the symptoms began to diminish after the third day some urticarial areas persisted for six days. Epinephrine 1:1000 by injection relieved the itching and resulted in an almost complete disappearance of the hives for about three hours. Ephedrine and Benzedrine orally had little effect. One week after the symptoms had disappeared skin tests with penicillin wheals appeared on the skin of the upper arm above the site of the skin test, the reaction being limited to the arm on which the tests were made. This reaction disappeared in about three hours and the author feels that it was not determined that the reaction was due to the penicillin or to an impurity in its preparation.

Four of fifty-six patients treated by Haswell and Wilkinson<sup>53</sup> developed serum-sickness-like reactions six to twelve days after their first injection. In all cases, the symptoms included a low-grade fever with malaise, a generalized urticaria and a patchy erythema. In some instances there was adenopathy, a transient edema of the eyes, mouth, and limbs and an anorexia. Although the penicillin differed in brand, cutaneous tests by patch, scratch, and intradermal techniques in all cases were negative.

Gordon<sup>49</sup> reports on three patients who respectively reacted with urticaria on the second, fifth and seventh days after the discontinuance of penicillin therapy, in all cases responding as well with pain and swelling of the joints, local warmth and painful motion, slight edema and tachycardia. In two cases the eyelids were swollen and in all three the last phase of the reaction was an exfoliative dermatitis of the palms of the hands. Epinephrine by injection controlled the hives in three, five and three days, respectively, with the arthralgia disappearing on the fifth and seventh days in two cases and persisting for ten days in the third. The dermatitis was the last reaction to disappear. The author believes that the type of reaction can be attributed to impurities in the penicillin and that it is an allergic reaction and should be treated as such, perhaps by desensitization.

Kendig and Toone<sup>54</sup> present three additional cases similar to Gordon's excepting that the patients were all of the same family, their reactions covering a period of six weeks. In none of these was there any exfoliative dermatitis; one patient had presented a mild urticaria several years previously, presumably due to egg, and a second had suffered from a trychophyton infection of moderate severity. The authors state that the course of the reaction may vary from five to fourteen days regardless of the treatment used.

In the five cases reported by Strakosch<sup>410</sup> the symptoms not only included those listed above but also abdominal cramps, and a secondary anemia with an increase in the sedimentation rate and a leukocytosis. The author suggests that in some cases the symptoms may resemble those of acute rheumatic fever and may lead to a false diagnosis. This series is interesting in that three of the patients gave local and constitutional reactions to skin tests with a commercial penicillin solution (50 U/0.01 c.c.). In one case the symptoms occurred four days after termination of a course of 1,200,000 U. of sodium penicillin given for a sore throat, with the urticaria disappearing in three days, the arthralgia in eleven and the lymph node enlargement in twenty-one days. A second course of 700,000 U intramuscularly seven weeks later caused, however, no ill effects.

In Eisenstadt's<sup>51</sup> two cases, the first had had a five-day course of penicillin therapy a month before the onset of his symptoms which arose eight days after the termination of a course of penicillin therapy given for pneumonia. In this patient, a skin test with a commercial penicillin preparation was negative three weeks later, the symptoms having subsided in six days. In the second patient, the penicillin had been given nine months previously, the symptoms occurring eight days after conclusion of a total of 100,000 U. followed two days later by a single injection of 100,000 U. in beeswax. The symptoms subsided in four days. The intradermal test with the commercial penicillin was positive, with that of the diluent being negative.

Mendell and Prose,<sup>54</sup> who treated more than 5,000 cases at a station hospital on Luzon with penicillin, reported only six cases (0.12 per cent) as being reactions sufficiently severe to require discontinuance of the drug. In four cases the reactions were suggestive of a drug allergy, whereas in two they were delayed and simulated serum sickness. The former cases demonstrated a pruritus, an erythematous rash, and edema and a fever with eosinophilia present in three, the symptoms subsiding within a few

days. In all cases, passive transfer precipitin and conjunctival tests were negative but patch tests were positive in all. The intracutaneous test was positive in two, while in the third it was positive with the brand of penicillin used, but negative with another brand. In the second series of two cases, reactions developed two to seven days respectively after termination of intramuscular penicillin therapy, both patients presenting symptoms of fever, generalized severe giant urticaria, pain and swelling of the joints, with dyspnea and wheezing occurring in one patient and requiring epinephrine for relief. Two hundred control subjects were tested to penicillin by the skin and conjunctival methods and then given 50,000 U. parenterally of the same brand of penicillin. The authors state that the intracutaneous and conjunctival tests were unreliable in predicting severe reactions, although patch tests might prove of value in detecting penicillin sensitivity.

A number of other reports of the same type have since appeared, all being similar in nature, and since they bring forward no new data, it was felt that they ought not to be either abstracted or listed.

Occasionally the reaction may be purely local, following injection as seen in the case described by Lederman,<sup>12</sup> whose patient took nine injections of penicillin in beeswax-peanut oil daily, but with the tenth injection developed a lump at the site and following the eleventh injection, presented red, hard areas around the sites of all of the previous injections. There was no pain, fever, or malaise. The patient was unable to tolerate various brands of penicillin in aqueous solution, once daily, as well as another brand of penicillin-beeswax-peanut oil in doses up to 7,500,000 units. There are no new infiltrations but the lumps from the first series of injections lasted over two months before gradually disappearing.

The patient described by Switzer<sup>12a</sup> reacted within one week to the first intramuscular injection of 1 c.c. of penicillin-beeswax-peanut oil, the local reaction being associated with a temperature of 100.2°F. Benadryl caused symptomatic relief, but the reactant area did not involute for almost two months. Since the patient had previously taken penicillin orally, it is suggested that she may have become sensitized to the penicillin, to an impurity or to the beeswax-peanut oil.

Blechmann *et al*<sup>9</sup> reported on two three-week-old twins, who each received twelve injections of penicillin-beeswax-peanut oil and who both presented indurations and tumors which ruptured spontaneously at the sites of injections in the gluteal areas.

Of special interest is the patient described by Call and Gilbert.<sup>14</sup> Four weeks after treatment of a cellulitis of the right hand with oral sulfadiazine and 320,000 U. of penicillin (intragluteally) the patient developed a large number of abscesses at the site of the penicillin injection. Four weeks later the patient was given intragluteal injections of 1,040,000 U. in the treatment of soft tissue wounds of the leg and again developed multiple abscesses of the buttocks with a large furuncle of the right leg four weeks later. He was given intramuscular penicillin for the treatment of these and again in three weeks developed a group of furuncles on the legs with abscesses at the site of the penicillin injections. Once more, intramuscular penicillin was given, to be followed in five weeks by abscesses at the site of injection. Following the use of penicillin for a fracture of the mandible the patient developed a furuncle, and intramuscular penicillin cured this furuncle, but ten days later it was followed by abscesses, at the site of injection. The furuncles showed a growth of staphylococcus aureus and the cycle of intramuscular penicillin and abscess formation was reported on two additional occasions. Intramuscular injection of 200,000 U. in sterile water was followed by the appearance of a sterile abscess at the site of injection. The diluent alone produced no reaction. Since the various courses of penicillin the case were given at different hospitals, the authors point out that contamination of penicillin as a factor in the abscess formation was highly unlikely. The conjunctival test was negative.

Since conjunctival tests have frequently been used as a method of proving penicillin sensitivity, the reports regarding eye reactions should be listed at this point. Early in 1946, Satulsky<sup>105</sup> reported on a thirty-one-year-old soldier diagnosed as having a severe chronic ulcerative keratitis of the right eye. Penicillin in a petrolatum lanolin ointment base (1,000 U/Gm.) was instilled into the affected eye and within a few hours the patient demonstrated a severe conjunctivitis with a dermatitis of the eyelid and the adjacent areas of the face. The ointment was discontinued and the symptoms subsided in several days. A patch test with the penicillin ointment and with crystalline penicillin gave no positive reactions, while the constituents of the ointment base were negative in reaction. The subsequent instillation of penicillin solutions (5,000 U/c.c.) produced a recrudescence of the symptoms.

Local sensitivity associated with a generalized sensitivity was reported by Welply<sup>138</sup> who treated himself with penicillin drops (1,000 U/c.c.) for a mild conjunctivitis. The eyelids became red and swollen with irritated margins, the condition clearing when penicillin was discontinued and sulfacetamide instilled. On two subsequent oc-

casions, penicillin therapy produced the same reactions. Of interest is the fact, however, that after an interval of some months when the patient was given local insufflations of penicillin-sulfathiazole powder for the treatment of an old mastoid sinus the eyelids responded with redness and swelling within twenty-four hours, the condition improving when the insufflations were discontinued.

Selinger's<sup>111</sup> patient developed a severe dermatitis of the eyelids five days after he began instilling a penicillin solution (250 U/c.c.) into each eye at two-hour intervals for a conjunctivitis. Schultz,<sup>107</sup> who reported on two of fifty-two patients treated with intraocular instillations of penicillin ointment or a solution containing 500-3,000 U/Gm (or c.c.), described a dermatitis of the eyelids in which the first disappeared when therapy was halted but flared up into an acute ocular dermatitis with three instillations of penicillin solution two days later, the scaliness persisting for five days. The second patient presented a contact dermatitis of the upper face and eyelids after two drops of the solution had been instilled every two hours for four days, the eruption also clearing within five days. Intracutaneous tests were positive in both patients, with patch tests positive in the second.

Pruritus alone as a side effect of penicillin therapy was described late in 1944 by Freyhan.<sup>42</sup> The patient had received 100,000 U. for ten days for the treatment of a pulmonary abscess. A severe generalized pruritus occurred five days after the administration of the antibiotic had been discontinued and then gradually subsided.

Not only may the patient respond with a pruritus without a rash, but he may also have a rash without pruritus as described by Holden<sup>56</sup>. The patient, a fifty-two-year-old male, with lobar pneumonia, who received 30,000 U. of penicillin every three hours for three days, developed a non-itching, non-papular rash spreading over the body. Passive transfer tests with penicillin produced wheals 2.5 cm. in diameter in a test subject as compared with areas of erythema, 0.6 cm. in diameter obtained with controls. The rash faded within three days and was followed by a five-day period of desquamation after discontinuance of penicillin treatment.

That the rashes may vary in type was seen by the report of Gent and Mackinnon<sup>16</sup> whose patient developed a morbilliform rash after the second injection of 30,000 U. of penicillin given at four-hour intervals for a tonsillitis. Rigor had followed the first injection and the rash followed the second. After discontinuance of penicillin, both abated.

An anaphylactic purpura following intramuscular penicillin therapy was described by Anderson<sup>1</sup>, in whose patient a second course of penicillin therapy consisting of 15,000 U. intramuscularly every three hours for a period of nine days caused a purpura associated with transient swelling of the joints and subcutaneous tissue and a toxic nephritis. The patient was treated with epinephrine by injection, by oral glucose and vitamin preparations, the symptoms diminishing in twenty-five days.

The patient treated by Vogel<sup>131</sup> for a pustulosquamous dermatitis with 250,000 U. of penicillin given intramuscularly every three hours developed a severe exfoliative dermatitis after the ninth dose. A second patient studied by the same author developed an edema of the face and a giant urticaria of the body following the topical use of a cream (100,000 U/60 gm. of a cetyl alcohol base) for twenty-four hours. Urticaria, as noted above, has been more often described as following intramuscular injections.

That a rash and urticarial reactions may occur together is suggested by the report of Gottlieb and Frankland,<sup>50</sup> whose patient, aged eleven, was given 5 daily injections intramuscularly of 2 c.c. 125,000 U. penicillin-beeswax-oil and who, on the eighth day of treatment, developed a swelling of the injection site, a slight edema and a generalized rash. Symptoms disappeared spontaneously four days after discontinuance of penicillin therapy.

The exfoliative dermatitis reactions may be extremely severe. Farrington and Tamura<sup>28</sup> reported on a seventy-eight-year-old white man treated with intramuscular penicillin for lobar pneumonia. On the fourth day the patient presented a generalized erythematous maculopapular eruption which, during the next three days, became a generalized diffuse erythematous vesicular eruption covering the entire body and followed by a widespread exfoliation of the epidermis and loss of the nails, receding over a period of four weeks. The patient responded to intradermal and contact tests with both the urticarial and tuberculin types of reactions. He reacted to different commercial brands of penicillin and to commercial penicillin K, but not to autoclaved material; to crude inactive extracts or penicillinase-inactivated extracts. Patch test with trichophyton, gliotoxin and streptomycin were negative, although an intradermal test with trichophyton was positive.

The patient may be sensitized by contact and react by injection as described by Shaffer.<sup>112</sup> A twenty-seven-year-old male with impetigo was treated with penicillin ointment (1,000 U/c.c.) petrolatum base. On the fourth day of the treatment the

patient developed coalescing vesicular lesions of the left cervical region and the right angle of the mouth, with an erysipiloid lesion appearing in two days on the area to which the ointment had been applied. Intramuscular injection of 30,000 units, three hourly, was instituted with no improvement of the lesions, but with the development of a severe pruritus and a generalized maculopapular eruption progressing within seven days to an exfoliative reaction involving the entire body. The impetigo cleared after treatment with ammoniated mercury. The author cautions against the use of penicillin ointments in the treatment of skin lesions.

The severe degree to which this exfoliative dermatitis may follow either injection or contact with penicillin and the various types of sensitivity which may occur are all seen in a patient described by Derzavis and Beinstein<sup>29</sup> whose 37-year-old white man, received a single injection of 300,000 units of penicillin in peanut oil for the treatment of a traumatic cellulitis of the right finger and a regional epitrochlear lymphadenitis. Six hours following the injection, the patient developed a generalized severe pruritus of the lower extremities followed by an acute erythematous eruption involving the extremities and genitalia, progressing to a hemorrhagic vesiculation during the next three to four days, the vesicles becoming ulcerated and gangrenous. The second type of reaction was shown on the tenth day when the temperature became elevated and a delayed serum-sickness type of reaction appeared. The dermatosis reached its peak between the twentieth and twenty-fifth days and gradually subsided with the healing of all of the lesions during the following month.

Such exfoliative dermatitis types of reaction may be delayed as described by Farrington *et al.*<sup>37</sup> There were no untoward reactions in a patient given 50,000 U. intramuscularly every three hours, using the amorphous commercial material for 5 days, after which there appeared a generalized erythema and twenty-four hours later, a typical erythematous generalized maculopapular dermatitis associated with intense pruritus, the rash being most marked in the axillae, groins, and flexures of the elbows. The patient's original eye condition had shown much improvement and the penicillin therapy was discontinued. At the end of forty-eight hours, the pruritus, erythema and rash had almost entirely receded. The patient was patch tested to 200,000 U. penicillin G on the upper right arm, the reaction site being negative at the end of forty-eight hours. An intradermal test (2.5 U. of crystalline penicillin G/0.1 c.c. of normal saline) produced an immediate erythema and an edema with an accentuation of the original injection wheal. There was a slightly elevated central edema that spread into pseudopodia, appearing within twenty minutes and receding in 1 hour. An accentuation of this reaction was noted in six hours and persisted as a tuberculin type of reaction for forty-eight hours. A control intradermal test with normal saline (0.1 c.c.) was negative. At the end of this time an exacerbation of the keratoconjunctivitis, which did not respond to topical sulfathiazole, suggested that penicillin therapy be resumed. It was used as a topical application (500 U/c.c.) of the amorphous penicillin in normal saline. There was improvement for forty-eight hours, following which an erythema, edema and vesiculation were noted on the periorbital region of the affected eye, the cheek and the adjacent areas of the face. A patch test with this material on the arm was negative, but on the angle of the jaw gave a 2-plus reaction in twenty-four hours. A repeated intradermal test with 200 U. of amorphous commercial penicillin on the right forearm gave no immediate reaction and was negative when seen at the end of forty-eight hours. Thirty-one days later the patient was retested by the intradermal method with 2.5 U. of amorphous penicillin, using the same brand and lot number, and reacted with an immediate reaginogenic type of reaction as well as a later tuberculin type of reaction at the end of forty-eight hours. A repeat patch test with 200 U. of the same amorphous penicillin gave a 2-plus reaction in forty-eight hours. Contact testing of the buccal mucous membrane with 200 U. crystalline penicillin G showed a moderate positive reaction after one hour of contact, persisting for twenty-four hours. The control contact tests were, all of them, negative.

The severity of such reactions is seen from the report of Morris and Downing<sup>30</sup> whose patient received 1,000,000 U. of penicillin for a postoperative infection. Itching of the left arm and hand was noted four days after the last injection, with an erythema and edema appearing twenty-four hours later; the edema being intense and progressing to the sixth injection day, at which time there were multiple ruptured and unruptured bullae, with multiple wheals affecting the left side of the face and the trunk. The bullous dermatitis disappeared in four to five days following bland therapy.

Since penicillin is derived from the mould *Penicillium*, it is not strange that relations to fungus infection should have been thought of early in the history of its use.

## PROGRESS IN ALLERGY

Lamb<sup>71</sup> treated a case of actinomycosis, which responded with a severe eruption and itching. Liberation of the toxins from the actinomycotic lesions may have caused the eruption. The patient gave positive reactions to intradermal tests with trichophyton and odiumycin, but not to penicillin. A second patient reacted positively to the intradermal test with penicillin but not to either trichophyton or odiumycin. Ten other control patients did not react to the intradermal tests with penicillin and the author suggests that all patients to be treated with penicillin should be questioned about the history of reactions to fungi. Those susceptible to the fungi should be tested intradermally with penicillin.

That some of the reactions may not be due to latent or associate trichophyton infection is suggested by Cornia<sup>27</sup> who elicited reactions in 2,000 soldiers as occurring in 0.5 per cent, one of the types of reactions being a simulating dermatophytosis. Of seven patients with fungus infections, who had never received penicillin therapy, fifteen gave immediate positive reactions to trichophyton; none showed a delayed reaction; eight showed immediate and delayed reactions to penicillin; and five only delayed reactions to trichophyton. The patients who reacted to the intradermal tests with three brands of the commercial penicillin sodium showed immediate positive reactions in an average of 57 per cent. In this group, patients previously treated with penicillin by intramuscular or unguent use showed no greater tendency to positive reactions than did others. The reactions were considered to be non-specific and due to impurities, although crystalline penicillin also gave positive skin tests.

On the other hand, Schnurman<sup>106</sup> described five cases of latent trichophyton activated by the use of penicillin. All of the patients had previously been treated for a trichophyton infection and then for a secondary condition requiring intramuscular treatment with penicillin. For a period varying from three to thirty-six months following the penicillin injections, there was a recurrence of the trichophyton infection (which had apparently been cured).

Kolodny and Denhoff<sup>60</sup> studied twenty-one immediate and 11 delayed reactions among 124 patients treated with sodium penicillin. The immediate reactions were seen in twenty-five per cent of the dermatological patients as compared with 6 per cent of the general medial or neurosyphilitic patients. Of the eighteen dermatological patients, seventeen had exacerbations of the pre-existent skin conditions with pruritus, hyperemia and serum exudation. In four, a vesicular, pruritic "id" eruption appeared on the hands and feet. The incidence of reactions was highest in those with an eczematoid dermatitis. The delayed reaction was the same in both groups of patients and was typical in that it included urticaria, giant swelling, facial edema, lymphadenopathy, arthralgia, myalgia and malaise. In these patients there was no apparent relation to previous penicillin therapy, although in four cases contact dermatitis followed the local application of penicillin to previously treated skin areas. Of the fifteen patients who reacted to intradermal penicillin, 11 showed immediate positive tests to 1,000-2,000 U/0.1 c.c. solution. Nine subjects reacted to tyrothricin and eight of these to penicillin. Of the fourteen non-reactors, only two were sensitive by skin test. The tyrothricin skin test was positive in a high proportion of the penicillin-sensitive individuals and the severest reactions are said to have occurred in patients with fungus infections. The authors classify the immediate reactions as a dermatitis medicamentosa and the delayed reactions as typically allergic in nature, with the active principle of penicillin as the incriminating agent.

The most careful studies done by Cornia and Lewie<sup>22</sup> elicited the relationships between sensitization to penicillin and pre-existing fungus disease. Following a series of eight experiments, the authors concluded that many of the local and systemic reactions occurring during or after penicillin therapy were the result of a previous sensitization by a dermatophyte. In forty-five children, aged two months to six years, who had never previously demonstrated fungus disease or received penicillin therapy, there was a non-specific immediate reaction after intradermal tests with 1,000 U. of penicillin, with no delayed forty-eight hour reactions. In seventeen patients, however, who presented active fungus disease, but had received no penicillin, immediate reactions occurred following intradermal tests with 41 per cent of the subjects, developing the forty-eight-hour tuberculin type of reaction. Of eight guinea pigs, five developed papular lesions following the second intradermal injection of penicillin given 28 days following the initial injection. In these five animals, the injection sites of the positive reactions were not flared up by intravenous injection of penicillin. There was no anaphylactic shock. Four of the five animals gave positive reactions to intradermal trichophyton injections. Five guinea pigs given weekly intradermal injections of trichophyton for four injections, followed a week later by intradermal injections of penicillin, did not develop sensitivities to either trichophyton or penicillin. A trichophyton gypsum infection in local in six guinea pigs resulted

in positive intradermal reactions to penicillin in three. In seven rabbits with trichophyton purpureum infection of the skin, five developed positive reactions to penicillin.

In a later paper, Cormia, Lewis and Hopper<sup>23</sup> evaluated the relationship between sensitization to penicillin and sensitization induced by superficial fungous disease by the Schultz-Dale test, using guinea pigs infected with *T. gypsum* or sensitized to penicillin. They demonstrated that in guinea pigs, anaphylactic sensitization to commercial sodium penicillin might be induced by a single injection given intradermally, or to crystalline penicillin sodium by a single intradermal, or four daily, intraperitoneal, injections. The guinea pigs could be sensitized anaphylactically to crystalline sodium penicillin G by infection of the skin with *T. gypsum*. These Schultz-Dale tests proved the presence of anaphylactic activity to commercial or crystalline sodium penicillin, in guinea pigs infected with *T. gypsum*. The authors feel that this positive reaction confirms the supposition that there is a common antigen in penicillin and the pathogenic fungi, which causes superficial fungous disease and that shock-like reactions in man are due to pre-existing sensitization by such pathogenic fungi.

The case of a very serious allergic reaction from penicillin is described by Gelfand,<sup>45</sup> whose patient, a twenty-eight-year-old woman, received penicillin for the treatment of a postpartum infection, the dose being 300,000 U. beeswax-oil, followed twenty-four hours later by 50,000 U. in saline, both given intramuscularly. Twenty-four hours after the first injection, the patient responded with fever, headache, listlessness, myalgia, arthralgia, skin rash, edema, bronchial asthma and subconjunctival hemorrhages. The administration of penicillin was halted and PBZ in doses of 50 mg. was given thrice daily. The patient was improved within twenty-four hours, being discharged six days after the use of the drug had ceased. There was no history of previous allergy or drug reaction, excepting for an epidermophytosis of the toes. In this patient, intradermal and passive transfer tests with penicillin were negative.

There are a number of references to the aggravation of bacterids by penicillin. Heinlein *et al.*<sup>54</sup> observed hypersensitivity reactions to penicillin in three patients with infectious eczematoid dermatitis, in three with eczema and in five with vesicular eruptions of the hands and feet, each with a history of symptoms of an underlying bacterial allergy, the symptoms being attributed to the rapid liberation of toxins from the focus of infection following vigorous penicillin therapy. In each case, the administration of standard doses of penicillin precipitated a hypersensitive reaction, aggravated the existing lesions and produced new eruptions. Although none of the patients in this series had received penicillin previously and all had proven negative skin tests for the antibiotics, in each the hypersensitive reaction occurred within a few hours or a few days after the initial dose. In one case there were positive skin tests to staphylococcus vaccine and to fungus extracts, but negative tests for penicillin. In a second there were positive tests with catarrhal and staphylococcus vaccines with a negative test to penicillin; the third, like the first, gave positive tests to the fungus extracts and the staphylococcus vaccine, but did not react to penicillin. The symptoms did not appear until the sixth day and included a leucopenia with a lymphocytosis instead of leucocytosis with a neutropenia.

Typical specific effects on bacterial responses are, of course, seen in Herxheimer reactions. Moore *et al.*<sup>87</sup> listed such reactions as occurring in 50 per cent of 418 cases of early syphilis. In Leifer's series<sup>72</sup>, the total was 87 per cent. In late syphilis, Stokes<sup>118</sup> reported forty-three (24 per cent) of 182 cases. In twenty-three of these, fever was the only reaction, but in several, transverse myelitis, Jacksonian convulsions, exacerbation of pain in tabes dorsalis, mania and hallucinations were seen. It is of interest that Herxheimer reactions have served to delineate the protean nature of lues, as seen by the case described by Scot and Clark<sup>108</sup> which demonstrates that "some clinical involvement of the kidney exists in early syphilis and that a focal Herxheimer reaction, affecting a subclinically involved renal parenchyma, may produce a nephrotic syndrome (syphilitic nephrosis)." The patient who had suffered a penile lesion on July 15 was admitted for antiluetic treatment on September the first, at which time he presented a generalized papular rash, the lesion being positive for *T. pallidum*. The physical examination was otherwise negative, there being no urinary abnormalities. The Kahn blood titer was 200 units and the cerebral spinal fluid negative. Treatment with penicillin was initiated, with 50,000 U. being given intramuscularly at two-hour intervals. Six hours after beginning treatment there was a temperature elevation; and again on the third day of therapy with nocturia on the second treatment day. The patient was given 4,800,000 U. of penicillin in eight days and five days after his discharge, demonstrated swelling of the legs and genitalia, at which time examination revealed a marked proteinuria, cylinduria, a low plasma albumin with inversion of the albumin-globulin ratio, massive edema, elevated blood cholesterol, subnormal basal metabolic rate and normal renal function tests, with no

hypertension, retinitis or hematuria. Following the use of a salt-free diet, the patient lost 30 pounds in five days with the disappearance of the edema, the urine becoming protein-free. It took about three months for the urine and blood chemistry to become normal, with the Kahn titer gradually declining to four units 130 days after hospitalization.

The case described by Cole *et al*<sup>19</sup> is interesting in that a Herxheimer reaction followed the first injection of penicillin and the authors not only describe local pain at the injection site, with urticaria, erythema multiforme-like eruptions on the extremities, but also an erythema nodosum-like eruption of the shins. Olansky<sup>95</sup> describes a severe febrile Herxheimer reaction in six patients following a single dose of 1,000 U. of penicillin. In three there was a diagnosis of secondary syphilis; in one congenital paresis, in one a gumma of the testicle, and in one later hypertrophic syphilides of the vulva.

Crawford<sup>24</sup> suggests that this reaction can be avoided by the administration of one-fourth or one-half the usual dose and by giving patients with late or complicated lues a course of bismuth prior to the penicillin therapy.

Penicillin can, of course, cause central nervous system effects. Early in 1945, Walker and Johnson<sup>124</sup> described convulsive effects following intraventricular injection in the treatment of meningitis. Preliminary studies show that penicillin, administered intracisternally, intraventricularly, and locally to the cerebral cortex in certain doses produces convulsive manifestations in mice, cats, dogs and monkeys. Penicillin from seven manufacturers was used with similar results, the intracortical injection of penicillin producing convulsive seizures in cats, monkeys and humans. Control injections with isotonic sodium chloride or 95 per cent alcohol caused no deleterious effects. The pH of the solution was not responsible and the convulsive seizures were apparently related to the high dosage. The convulsive factor was affected by aging, boiling, and the level of dosage in man was about 20,000 U., which produced electroencephalographic changes but no clinical symptoms. Ten thousand units injected near the motor area produced twitching of the face and hands for three hours. The authors feel that injections of penicillin into wounds or abscesses may, however, prevent the diffusion of the drug to the adjoining nerve tissue. The convulsive factor may, on the other hand, limit the amount of penicillin injected into the cisterna magna and the cerebral ventricles.

The problem is reviewed by Walker, Johnson and Kollnos,<sup>125</sup> who describe penicillin given intrathecally in high concentration as causing multiple hemorrhages, severe inflammatory reactions and transverse myelitis. They review other effects such as peripheral neuritis and convulsions as observed in a patient with a latent epilepsy, who had specific electroencephalographic changes. This subject was given penicillin intramuscularly for an incidental condition. The authors state that toxicity is manifested by an acute necrosis involving the adrenal glands, particularly the cortex and suggest that some of the unexplained deaths in human beings occurring during the administration of penicillin may be of this type since the autopsy findings, in a few instances, do not mention adrenal damage. They quote Furth as suggesting that functional impairment of the adrenals may precede objective evidence of damage and may cause death without the confirmation of definitive pathological findings. According to Sweet *et al*<sup>122</sup>, mild and severe radiculitis may follow intrathecal injections of penicillin, with all of the patients making a full recovery.

In Simon's case<sup>116</sup> the patient, a five-day-old infant, was prepared for the removal of an meningomyelocele with 100,000 U/20 c.c. saline being placed in the subarachnoid space. A second injection of 100,000 U. twenty minutes later into the lumbar muscle was followed by convulsions, cyanosis, and apnea. The symptoms were controlled by the administration of oxygen, which was given for three hours. Consciousness was restored at this time and attributable by the author to the depletion of the penicillin in the blood. Neymann (in a discussion of a paper by Johnson *et al*<sup>120</sup>) states that intraventricular and intracisternal injection of penicillin in man may induce a status epilepticus with a fatal outcome. In a later paper, Walker and his co-authors<sup>123</sup> call attention to the toxic effects of penicillin on the nervous system, showing that although electroencephalographic findings were normal in 40 per cent of fifty-one cases receiving systemic penicillin for conditions other than those primary to the central nervous system and although there appears to be a relatively wide margin of safety between the antibiotic concentration and the convulsive threshold of penicillin and also streptomycin, the toxic effects of penicillin and of other antibiotics on the nervous system must be taken into consideration. Tests with actinomycin and clavacin, as well as with streptomycin and streptothricin all produced convulsive manifestations when injected into the cerebral cortex of cats or monkeys. Epileptic attacks have been produced in monkeys by application of 250 units to the cerebral cortex.



According to Kolb and Gray<sup>68</sup> intramuscular administration of penicillin may cause localized peripheral neuritis as seen in seven cases. The neuritis occurred from ten to twenty-one days after the initial injection and after ten to seventy-two injections representing a dose of 200,000-2,000,000 units. Both sensory and motor disabilities were observed in three cases affecting the peroneal nerve, in one the sciatic nerve and in two the nerves of the brachial plexus. All injections were given in the gluteal and thigh regions. In only one instance could the neuritis have resulted from the direct infiltration of penicillin into the nerve itself. Sensory function was recovered in eight weeks; motor function in four months, although motor weakness persisted for seven months in the patients with brachial palsy. No evidence was observed that the neuritis was related to the brand of penicillin used, to compression or to allergy to penicillin.

Erickson, Masten and Suckle<sup>36</sup> described the complications of intrathecal use of penicillin and added their four cases of serious reactions to those in the literature, suggesting that such complications may be avoided by using dilute solutions, with the number of intraspinal injections being kept at a minimum, with greater reliance being placed on early treatment with maximum doses of penicillin given parenterally. Morgan<sup>69</sup> lists the intrathecal reactions as including headache, vomiting, vascular collapse, cyanosis, convulsions, unconsciousness, flaccid paralysis of the extremities, with increased spinal fluid cell count and protein values.

That toxic psychoses may result from penicillin therapy is demonstrated by the report of Kline and Highsmith<sup>67</sup>, whose patient, an eighteen-year-old girl, received penicillin for the treatment of an upper respiratory illness, 48,000 U. being given intramuscularly in thirty-six hours. One year later, for the treatment of an otitis media, she received 420,000 U. intramuscularly and 3,800,000 U. orally in ten days. Two days after conclusion of the second course of treatment she was re-admitted to the hospital with a temperature of 101°F, generalized urticaria and an arthralgia of the fingers, knees and ankles. The neurological examination was negative. The urticaria responded to the administration of PBZ every four hours, the arthralgia subsiding after novocaine injections. On the fourth hospital day, the patient became restless, suspicious, and complained of hearing voices. Although the PBZ was discontinued with an exacerbation of the urticaria the mental symptoms became more pronounced. With the re-institution of antihistaminic treatment, the hives subsided and within two days the mental symptoms disappeared. The authors feel that the mental symptoms were due to edematous lesions of the brain resulting from a localized penicillin sensitivity.

It is essential to realize that secondary reactions affecting the blood and urine may confuse the laboratory studies in patients receiving incidental antibiotic treatment. Macht<sup>77</sup> has demonstrated that streptomycin and all brands of amorphous penicillin produce a marked acceleration in the clotting time of the blood in rabbits and cats, irrespective of the means of injection, with penicillin G having only a slight thromboplastic effect, K a still greater and penicillin X the greatest effect. A small amount of penicillin X has a synergistic effect when injected in a mixture with penicillin G. The effect is usually seen fifteen to twenty minutes after injection, but may be delayed one hour. In rabbits, the clotting time is shortened for long periods, but usually approximately one hour. This thromboplastic action may be neutralized by Dicoumarol administered orally. Fleming and Fish<sup>39</sup> have shown the coagulation time of human blood *in vitro* is increased and contraction of the clot retarded by both crystalline and impure penicillin. The greater the concentration in the blood the longer the coagulation time. The results, however, do not pertain to systemic administration of penicillin because with such therapy the concentration of the drug is very low. The local administration of penicillin in concentrations exceeding 100 U/ml might interfere with coagulation and clot contraction.

Although not completely conclusive a paper by Spain and Clark<sup>117</sup> demonstrates the possibility of agranulocytosis occurring during a course of therapy in a patient in whom penicillin was given preoperatively and postoperatively for a cecostomy. The third day postoperatively the patient demonstrated a generalized erythematous macular rash, with a temperature rise to 104°F, with a white cell count which dropped from an initial 13,150 to 2,800 and then to 100 by the fourth day. Penicillin was discontinued, a blood transfusion given and sulfadiazine substituted for the antibiotic agent with a rise in white cell count to 6,000 and a temperature drop to 101°F within sixteen hours. The patient died on the third day. The autopsy revealed no abnormalities of the bone marrow. The authors feel that although the relationship is inconclusive, the signs point to penicillin as being the causative agent.

Although reactions in large variety have followed penicillin therapy, some may, of course, not be due to penicillin. In a few instances, the relationship to other causes



was known or could be surmised. Of the number of such, the following miscellaneous additions have been chosen.

In 1946, hepatitis was described as being a sequel to penicillin injections. As described by Howells and Kerr<sup>58</sup> the period between injections and the onset of icterus ranged from sixty-two to 157 days, with an average of ninety-seven days. The jaundice lasted from ten to forty-four days with an average of twenty-one days, and the period of hospitalization was fifteen to forty-nine days, with an average of thirty days. Hughes<sup>59</sup> described the development of infectious hepatitis in twenty-three of 144 patients and in ten of sixty-six patients being treated with penicillin injections for bone infections. The syringe was found contaminated with red blood cells, due either to back pressure from the contracted muscle, spread of blood from the needle to the syringe or suction when removing the needle from the syringe. Since injections had been given to several patients with the same syringe, with only a change of needle, it is possible that one patient could be infected with hepatitis from another. Of the 124 cases of hepatitis admitted, thirty-six had received penicillin injections within the preceding seven months. In ten cases, it was possible that the jaundice was post arphenamine or hemologic serum jaundice, but in 21 per cent of twenty-six cases, the jaundice was considered as subsequent to the penicillin treatment.

Other types of secondary reactions may follow penicillin injections as seen in the report of Ebrill and Blek<sup>33</sup>, whose patient, an eleven-year-old boy, receiving penicillin by continuous intramuscular administration for the treatment of a large, painful abscess of the right axilla developed a tuberculous abscess at the point of the injection. There was no possible source of tuberculous infection in the patient and it was concluded that the tubercle bacilli had gained access to either the penicillin powder, the solution or the injection apparatus through the faulty technique of the individuals preparing them.

The cases reported by Harris *et al*<sup>52</sup> describe a bacillus pyocyaneus infection occurring in four patients, who received penicillin treatment. The first, a patient with pneumococcus (Type 18) meningitis received penicillin intramuscularly and intrathecally with a return of temperature to normal and with a subsequent elevation. The postmortem examination showed the spinal fluid culture to contain *B. pyocyaneus*. The second patient presented a similar clinical course, as did the third and fourth, who, however, survived. It is discovered that a closed jar used to store sterilized syringes used for the intramuscular injections of penicillin harbored *B. pyocyaneus*. The syringes became contaminated and therefore contaminated the stock penicillin used. No abscesses, however, occurred at the site of intramuscular injection in any of the cases. The authors suggest that syringes be kept separate and autoclaved, that individual vials of penicillin and of saline be used for each patient, and that the caps of the vials be washed with individual iodine and alcohol swabs before being punctured.

The case described by Mitchell, Pordy and Wallach<sup>55</sup> concerns the occurrence of a bacillus welchii, gas gangrene at the site of penicillin intramuscular clysis in a fifty-one-year-old woman who was found to possess a positive blood culture of *Staphylococcus aureus*. Eighteen days after initiation of treatment the site of penicillin infusion showed tender, swollen, hard, crepitant fluctuant masses, the culture from which yielded *B. welchii*. The patient was given gas gangrene antitoxin and the area widened and treated locally with hydrogen peroxide, penicillin instillations and packs, responding to treatment.

Since penicillin in oil or beeswax is being used in decreasing amounts, the reactions due to the composition and method of administration can well be omitted at this time, excepting to remind ourselves that pulmonary embolism may follow such treatment. The patient described by Bondy *et al*<sup>11</sup> was an eighteen-year-old negress suffering acute pulmonary distress evidently owing to an obstruction to the flow of blood through the pulmonary vascular bed within twenty-four hours after an accidental intravenous injection of 2 c.c. of a mixture containing 600,000 of penicillin calcium suspended in peanut oil containing 4.8 per cent white wax. This led to animal studies which indicated that peanut oil and peanut oil-miner oil could be demonstrated in the capillaries of the lung while the beeswax mixture was trapped in the larger branches and pulmonary arteries. The animals were sacrificed at intervals of five minutes and twenty-four, forty-eight and seventy-two hours after the intravenous injection of the various mixtures and it was shown that the most severe emboli were produced by the beeswax mixture. The granuloma produced by the beeswax-peanut oil mixture resembled that produced by lipoid pneumonia. The animals given fatal doses of peanut oil exhibited cerebral involvement, while lethal doses of peanut oil-beeswax produced pulmonary edema without evidence of peripheral emboli.

It was known in 1945 that massive doses of penicillin caused highly positive quali-

tative albumin reaction in rabbits, who received massive doses of penicillin, although they had previously demonstrated negative albumin urinalysis. Perlstein *et al*<sup>107</sup> state that the addition of 25 per cent, by volume, of acetone or ethyl alcohol to 5 c.c. of urine will prevent these pseudo-albumin reactions, providing that less than 10 to 13 mg. of penicillin is present in the urine. Pseudo-glycosuria has also been described as sequential to penicillin therapy by Boldref<sup>10</sup> who describes two patients both of whom gave positive urine sugar reactions. The author demonstrated that a penicillin solution, 100 U/c.c. reduced the copper sulfate of Benedict's solution *in vitro*. Nylen<sup>12</sup> warns that impairment of renal function should be watched for in the course of penicillin therapy on the basis of a patient whose partial anuria following sulfadiazole treatment progressed to complete anuria with penicillin therapy. Such reactions, if true, must indeed be rare.

For a physician confronted with a case of penicillin sensitivity the paramount problem is one of treatment. He is faced with two problems, the patient's original illness which requires penicillin therapy and the reaction to penicillin which needs treatment in its own right. Unfortunately, the reactions of penicillin are so profound in their nature, the types of penicillin so many and the variation from lot to lot and from manufacturer to manufacturer so different that no clear-cut definite method of treatment, applicable to all patients and all types of reactions, exists. The problem is especially complex because new types of penicillin and new methods of administration appear with bewildering succession, each claiming to be more free of reactions than its predecessors.

In five patients studied by Callaway and Barefoot<sup>15</sup> search was done for evidence of the presence of penicillin antibodies in cases of urticaria. All intracutaneous and passive transfer tests were negative, although in the precipitin tests in all instances, including the control tests, a fine precipitate was noted at the junction of the serum and penicillin solutions. The authors state that the results were inconclusive and also, since in all instances the urticaria was controlled by Benadryl, the hives may be explainable as due to the presence of an excessive amount of histamine, but from the studies reported, not present as an antigen-antibody reaction.

Farrington and Tamura<sup>33</sup>, however, describe immediate urticarial reactions to intradermal tests with crystalline penicillin G and K. The reaction appeared two to five minutes after injection and consisted of an accentuation of the original injection wheal, manifested by a slight central edema and a spreading erythema usually receding in an hour. The authors state that they have encountered no associated generalized urticaria or constitutional symptoms with the method, the immediate reaction of this type proving helpful in about 24 per cent of the cases. The authors stress the point that correlation of cutaneous testing, penicillin therapy and reactions depend upon many factors, including the site, the rate and the number of antibodies formed and suggest that testing be done with diluted solutions, the degree of sensitivity being ascertained by quantitative tests using 2.5-2,000 U/0.1 c.c. normal saline. They believe that a significant degree of sensitivity is indicated by a reaction with a diameter over 1.5 cm. with 2.5 U of crystalline penicillin. The truly positive immediate reaction is almost invariably followed by hypersensitivity reactions to penicillin in therapeutic doses. Simultaneous testing with various penicillin products indicate the one most likely to be tolerated.

Although the penicillin-oil-beeswax type of treatment is no longer in general use, the question of sensitivity to the medium is worthy of brief mention. According to Gay<sup>44</sup> the beeswax is not antigenic. On the other hand, Watson<sup>237</sup> has shown that a bee keeper who was given six injections of 250,000 U. penicillin-oil-wax for the treatment of a carbuncle, responded on the eighth day after the first injection with reactions of the sites of the old bee stings, although she had not reacted to an aqueous solution previously given her.

That sensitivity may be associated with different lots of the drug is illustrated by the report of Barefoot and Orlansky<sup>3</sup>, whose patient responded with urticaria to non-crystalline penicillin therapy responding six hours following the first injection with an urticaria followed in twenty-four hours by generalized erythema lasting twenty-four hours more. Ten days later the patient developed a generalized furunculosis and non-crystalline sodium penicillin treatment was resumed with 20,000 U. every three hours, the patient responding after five doses with generalized erythema and edema of the skin and an exacerbation of a chronic tinea cruris and a chronic dermatophytosis. Skin tests with crystalline and non-crystalline penicillin in 1,000 U/c.c. in saline showed a 2 cm. area of erythema with induration to the first, with none to the second. The patient was given crystalline penicillin every three hours with no untoward effects. The authors report three other patients who could not tolerate non-crystalline penicillin but could take crystalline penicillin G.

Peck and his associates<sup>96</sup> described an apparent successful desensitization to penicillin in a sixty-three-year-old male who responded to intramuscular penicillin by an erythematovesicular eruption appearing on the hands, feet and groin, rapidly becoming generalized. In this case, intradermal tests with crystalline penicillin were positive. The patient was given subcutaneous injections of penicillin three times weekly, beginning with a dose of 400 units and doubling each dose until 12,000 U. was being injected by the end of the second week, the dose gradually being increased to 20,000 U. After provocative intramuscular injections of 5,000; 10,000; and 30,000 U. were given without untoward effects, a treatment regimen of 30,000 U. three hourly, was begun. A cutaneous reaction appeared after the fourth injection. The penicillin was discontinued for forty-eight hours and then resumed in smaller doses of 10,000 U/3 hourly, the dose being taken by the fourth day to 30,000 U, which was continued at this level at three-hourly intervals for seventeen days without reaction. Skin tests at that time to both crystalline and commercial penicillin were negative.

Desensitization has also been used for contact dermatitis<sup>103</sup> injections of 0.05 c.c. of a solution containing 10 U. c.c. being given thrice weekly, increasing the dosage gradually as in pollen desensitization. After a dose of 1 c.c. is reached with the 100-unit/c.c. solution, increasing concentrations of 1,000; 10,000; and 100,000 U/c.c. should be used. If a dermatitis develops during treatment, the dose should be reduced. The application of a PBZ-containing ointment before having penicillin may prevent the development of the dermatitis.

Intravenous nicotinic acid in doses of 35 mg. in 10 c.c. of distilled water has been reported by Service<sup>112</sup> as controlling urticaria in forty-one cases of penicillin sensitivity. The antihistaminic drugs have all been used with varying success. Wilecox<sup>140</sup> treated six cases of urticaria with Benadryl in doses of 50 mg. t.i.d. In four cases the urticaria cleared in one to three days, although the usual severe reaction lasted four or more days. One patient was treated successfully with ephedrine. In one case, however, the concomitant use of Benadryl and epinephrine caused collapse and both drugs had to be discontinued. Dean's patient<sup>28</sup>, who had responded with urticaria, pruritus, dyspnea, enlargement of axillary and inguinal glands and an expiratory wheeze, was rapidly relieved by the oral administration of 100 mg. of Benadryl, as an initial dose, followed by 50 mg. six hourly.

A patient described by Kampmeier<sup>61</sup> had reacted to a third course of penicillin therapy with pruritus, urticaria and edema of the hands, an intradermal test to the penicillin used being positive. PBZ in the 40 mg. dose two hourly, given orally, controlled the edema in four hours, making the patient asymptomatic in twelve hours.

Gelfand<sup>15</sup> also used PBZ in 50 mg. doses after an initial 150 mg. with improvement noted in forty-eight hours.

In Barach's<sup>2</sup> series of 51 patients treated for pulmonary conditions with the aerosol type of therapy, treatment for unfavorable reactions is noted as being controlled by PBZ, Benadryl or Vitamin K. An increase in dyspnea as a reaction to the aerosol penicillin was treated by substitution with systemic injection therapy. Lubowe<sup>74</sup> treated a severe diffuse erythematous maculopapular eruption, involving the face, chest, back and extremities and associated with a marked area of induration and swelling at the site of injection in a patient given 300,000 U/crystalline penicillin G in beeswax-peanut oil with Thephorin in doses of 200 mg. daily with complete disappearance of the symptoms after five days.

The number of cases in which the antihistaminic agents do not have any effect are rarely reported. In the author's own personal experience with urticaria and angioneurotic edema following procaine penicillin G suspended in peanut oil containing 2 per cent of aluminum monostearate no alleviation of symptoms occurred following the ingestion of 500 and 100 mg. doses of PBZ, Thephorin, therylene, Neohetramine, Decapryn, with mild alleviation following ingestion of Trimeton. Demerol in 50 mg. and 100 mg. doses given subcutaneously was the drug which controlled the associated pruritus, having no effect upon the urticaria or angioneurotic edema, which lasted five days.

The two cases described by Davis<sup>27</sup> also failed to respond to anti-urticarial drugs of either the antihistaminic or sympathomimetic type.

Rossellini and Van Rooy<sup>101</sup> reported a delayed reaction to penicillin in oil and wax as treated with procaine intravenously, 1 gm. in 500 c.c. of isotonic saline being given in two hours. After the second infusion, the following day the patient was symptom-free. The symptoms had lasted for three days before treatment had started and since the average case of urticaria lasts approximately five days, all reports of successful treatment must take this into consideration. In the patient described by Dressler and Dwork<sup>31</sup> the patient reacted with urticaria and fever to a second course of penicillin, the symptoms not responding to 250 mg. of Benadryl given in divided doses.

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The symptoms included a rash, generalized pruritus, sore throat, arthralgia, and a high leukocyte count. Calcium gluconate and epinephrine had no effect, but 1 gm. procaine and hydrochloride in 500 c.c. of isotonic saline by intravenous drip resulted in the disappearance of all the hypersensitivity symptoms in twenty-four hours. Cutaneous tests to penicillin sensitivity given nine days later were negative.

Cohen and Kaufman<sup>17</sup> also used the State and Wagensteen Method of treating penicillin sensitivity with procaine hydrochloride, two of their four cases not responding. One patient, who developed angioneurotic edema, urticaria, myalgia, arthralgia and fever ten days after having taken penicillin did not respond to Benadryl, PBZ, intravenous calcium thiosulfate, Vitamin B, Vitamin K, Demerol, phenobarbital, atropine, codeine, aspirin, intravenous nicotinic acid, intravenous glucose, autohemotherapy, or procaine hydrochloride. Repeated injections of epinephrine alone gave temporary relief. In the second patient, intravenous calcium gluconate relieved the itching, although Benadryl and intravenous procaine were of no benefit.

Waldrott<sup>132</sup> warns that a possible fatal reaction may follow the use of procaine in sensitive subjects. One patient was given 0.5 Gm. of procaine hydrochloride in 250 c.c. of saline solution intravenously developed a severe allergic shock. Patients with chronic urticaria are most apt to be sensitive to the drug and the preliminary skin tests are unreliable when the skin is the site of urticarial lesions.

At the present time information concerning penicillin reactions may be summarized as follows: "The reactions occur most frequently in patients who have had several courses of penicillin. The continuation of penicillin treatment of a patient who has reacted with urticaria may or may not be tolerated. Skin tests are unreliable in predicting the occurrence of reactions and the antihistaminic drugs may or may not control the reactions and permit continuation of penicillin therapy." Pillsbury and his associates<sup>30</sup> state that the urticaria reactions may be persistent and severe and may be accompanied by asthma and may be followed by ecchymoses and uterine bleeding. It is their opinion that the incidence of urticarial reactions is increasing as suggested by the fact that 1.8 per cent of reactions occurred in the first 824 cases of syphilis treated at the University of Pennsylvania, whereas twelve cases have occurred in the last 200 patients treated between October, 1945 and May, 1946. Of twenty-three cases of urticaria treated with antihistaminic drugs, sixteen with Benadryl were relieved in fourteen; with no relief in two and seven treated with PBZ showed relief in two and none in five. In their opinion, penicillin must be halted as soon as a reaction occurs, unless there is immediate critical need of the drug. Antihistaminic agents should be given by mouth three times daily or slow intravenous injection in isotonic saline is advised if the reaction is severe. After subsidence of the urticaria or the accompanying symptoms, a test dose of another brand of penicillin (1,000 U.) may be given, while the antihistaminic drug is continued by mouth. If there is no reaction in six hours, a second dose of 10,000-20,000 U. can be used followed by the full therapeutic dose if there is no reaction within four hours. The antihistaminic drugs should be continued and gradually reduced over a period of two to three days. No compounds prolonging the serum level of penicillin should be used during the period of trial administration. If re-administration is impossible and therapy is desirable, cautious administration should be resumed after an interval of four or more weeks.

It is, of course, too soon to judge the new types of penicillin, although preliminary reports for penicillin O indicate that it is probably less sensitizing than the other types now generally available. It is hoped that future studies and reports will be made by physicians trained in the field of allergy and immunology and familiar with the technique for testing sensitivity, defining it if such sensitivity occurs. A number of the earlier papers are confused and unreliable because they were made by the physicians using penicillin for the treatment of infectious conditions. These workers were only secondarily expert in recognizing and testing for sensitivity. It is hoped that future studies will be done by experts in the field of allergy. Had this course been followed, a great deal of time would have been saved and a great many patients spared reactions.

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# News Items

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## CHICAGO SOCIETY OF ALLERGY

We are pleased to announce that at the meeting of the Chicago Society of Allergy on May 19, 1948, the following officers were elected: President, Dr. Edward G. Tatge; Vice President, Dr. Morris A. Kaplan; and Secretary, Dr. Theron G. Randolph.

## DIVISION OF MYCOLOGY, NEW YORK ACADEMY OF MEDICINE

The Division of Mycology of the New York Academy of Sciences held its inaugural meeting on October 22, 1948. Dr. Norman Conant, Duke University, gave a lecture on "Sporotrichosis, Clinical, Epidemiological and Immunological Aspects of the Infection."

The following officers were elected: President, Dr. Frederick Reiss, New York University School of Medicine, and Secretary, Dr. Royal M. Montgomery, Polyclinic Hospital.

## COURSE IN ALLERGY

The Hansel Foundation and the American Society of Ophthalmologic and Otolaryngologic Allergy conducted a Course in Allergy as related to Otolaryngology, December 6 to 11, in St. Louis at the Sheraton-Coronado Hotel.

Instruction was given in office management, history taking, skin testing, microscopic study of nasal smears, pathologic specimens, and pollen grains. The preparation and dilution of extracts for treatment and skin tests was also demonstrated. The course was well attended by members of the Society as well as other nose and throat specialists.

## AVAILABLE RESIDENCIES

There are two residencies available in allergy effective the first of January and the first of July. One at the Veterans Administration Hospital (Dean's Committee Hospital) at Aspinwall 15, Pennsylvania, and the other at the Medical Center University of Pittsburgh School of Medicine. Opportunities are provided for in-patient and out-patient care, training in allergy and dermatology, instructions in botany and immunology, preparation of extracts and facilities for clinical and laboratory investigation.

Address all inquiries to Leo H. Crip, M.D., May Building, Pittsburgh, Pennsylvania.

## SOUTHEASTERN ALLERGY ASSOCIATION BULLETIN

The fourth annual meeting of the Southeastern Allergy Association will be held at the Washington-Duke Hotel, Durham, N. C., on Saturday and Sunday, January 22 and 23, 1949.

Plans for the program are progressing nicely. Dr. George Rockwell, president of the American College of Allergists, and Dr. Walter Winkenwerder, president of the American Academy of Allergy, are to be the guest speakers. There will be a panel on "Infectious Asthmas" headed by Dr. Osear Swineford and a panel on "Food Allergies" headed by Dr. Hal Davison.

This year the program committee is asking for two volunteers to present papers at the afternoon session. These papers will have to be limited to 20 minutes, with 10 minute discussions. Anyone desirous of presenting a paper, please get in touch with the secretary at once.

Saturday noon there will be an informal luncheon for members. Saturday night



## NEWS ITEMS

there will be the regular banquet, to be held at the Washington-Duke Hotel. As usual, this will be the time for all the wives to renew their acquaintances, so be certain to bring your wife.

Hotel reservations should be made directly with the hotel—and it is suggested that this be done early!

Those planning to attend are requested to write Dr. Katherine B. MacInnis, 1515 Bull St., Columbia, S. C., for particulars.

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The next issue of the ANNALS OF ALLERGY will announce the first volume of "Progress Notes in Allergy." These have appeared during the past five years in the ANNALS and have been greatly in demand. This volume will have a neat binding and will be sold at a popular price.

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Dr. David Ordman, F.A.C.A., of the South African Institute for Medical Research, Johannesburg, South Africa, has commenced to organize an allergy society in South Africa for the purpose of joining the International Association of Allergists, Inc.

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Dr. J. H. Frazer, who has served for many years as Medical Director of the Arlington Chemical Company, Yonkers, New York, and who has been a familiar figure at the various national allergy meetings, as well as the scientific exhibits featuring allergens, has retired and is now residing at 146 West 79th Street, New York 24, New York.

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Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, New York, are the sole agents for the new journal, *Acta Hematologica*, published by S. Karger, Basel, Switzerland. This will be of considerable interest to hematologists in the light of the growing importance of hematology. There is an imposing array of editors and collaborators representing hematologists from all parts of the world.

\* \* \*

Dr. W. Randolph Graham, who for many years was a partner in the Vaughan-Graham Clinic and later the Graham-Thomas Clinic, has established the Graham Allergy Clinic, 201 West Franklin Street, Richmond 20, Virginia, and is the director, limiting his practice to allergy and internal medicine. Doctor Graham will continue a training school of allergy technology and postgraduate training as fellowships and residences in allergy. Dr. William J. Kucewicz is associated with Doctor Graham.

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At the inaugural meeting of the Section of Allergists of the Hungarian Medical Trade Union, Association of Physicians, was held on March 4, 1948, the following officers were elected: Chairman, K. Hajos; Vice Chairman, E. Rajka; Secretary, L. Mosonyi.

The aim of the Section of Allergists is to promote cordial relations among the Hungarian allergists and to organize scientific meetings and postgraduate courses. With the purpose of promoting international relations, the Section of Allergy has joined the International Association of Allergists.

# BOOK REVIEWS

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**DISEASES OF THE EAR, NOSE and THROAT.** By William Warson, M.D., with a foreword by Arthur W. Proetz, M.D. 772 pages, 11 figures. Price \$8.50. New York: Appleton-Century-Crofts, Inc., 1948.

The author's position as professor of otolaryngology and attending otolaryngologist at the New York Polyclinic Medical School and Hospital, et cetera, makes this book authoritative in every respect. It is an epitome of material gathered and organized for his teaching the past twenty-three years.

The first section of the book deals with such general considerations as the taking of the history, the necessary equipment for the usual physical examination, the safe use of local anesthetic drugs and vasoconstrictor medication, and local and general anesthesia. This is followed by a chapter of general information on chemotherapy with the sulfonamide drugs and the antibiotics.

In each of the following sections there is a brief review of the essential points in the surgical anatomy, followed by a full consideration of physiology of the parts concerned which is essential to restore normal function. The etiology, pathology, signs and symptoms are concisely pictured.

The illustrations have been drawn by the author and are clear, simple and accurate. The last chapter is followed by a formulary of prescriptions for medications to be used by the patients. There is an excellent chapter on the allergic diseases of the respiratory tract.

The book is up to date, is characterized by its simplicity, and is an ideal reference book for both the student and the experienced specialist.

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**DIRECTORY OF PHYSICIANS INTERESTED IN CLINICAL ALLERGY**  
Compiled by Dr. Jonathan Forman. 178 pages. Cloth binding. Price \$4.00  
orders of 5. Published by the International Correspondence Society of Allergy, 1948.

This book embraces a wealth of information, including requirements for membership in the American College of Allergists, the American Academy of Allergy and the American Society of Certified Allergists. It contains an index of the allergists in the United States and those outside of the United States.

Orders should be sent in at once, since only a limited number of copies was printed. Orders should be addressed to Dr. Jonathan Forman, 956 Bryden Road, Columbus 5, Ohio.

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## RELIEF OF ASTHMA BY MEANS OF LOW MELTING POINT SUPPOSITORIES

*(Continued from Page 674)*

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# ABSTRACT

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## EXPERIMENTAL STUDY OF PURPURIC MENINGOCOCCEMIA IN RELATION TO THE SHWARTZMAN PHENOMENON. B. Black-Schaffer, Arch. Path., 43:28-54, (Jan.) 1947.

Three experiments were carried out to investigate a possible relationship between the Shwartzman phenomenon and purpuric meningococemia.

Experiment 1 served to confirm and elaborate the fact that twice-washed meningococci, both living and dead, possess potent preparatory, and provocatory substances capable of producing the local Shwartzman phenomenon.

Experiment 2, by comparing the preparatory potency of eighteen meningococcal strains, demonstrated that most of the strains (five of eight) associated with purpuric meningococemia fall into a unique and very potent group. The strains obtained in cases of nonpurpuric meningitis produced less of the preparatory factor.

In serologic group distribution the two categories of meningococci were essentially identical.

Bilateral necrosis of the adrenal glands with hemorrhage was found in two animals of Experiment 2.

Experiment 3 was designed to test the response of rabbits to meningococemia maintained, if necessary, over a period of twenty-four hours. General cutaneous purpura was produced in a number of animals. In addition to the cutaneous lesions, one rabbit displayed marked adrenal necrosis and hemorrhage: Waterhouse-Fredrichsen syndrome.

The close relationship of the general purpura to the local Shwartzman reaction was illustrated by the simultaneous appearance of both in rabbits which, previous to their meningococemia, had been prepared in one or two sites by intradermal inoculation of meningococci.

Many of the animals of Experiment 3 disclosed at autopsy bilateral renal cortical necrosis. Since in rabbits this lesion is recognized as characteristic of the generalized Shwartzman reaction, it is evident that washed meningococci are capable of producing not only the local but also the general phenomenon.

It is believed that the Shwartzman substance acts directly or indirectly on the interlobular arteries of the kidneys, causing marked vasoconstriction and thus initiating the sequence of events leading to bilateral renal cortical necrosis.

*Duke University Medical School  
Durham, North Carolina*

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Abstract of paper presented at the third annual meeting of the American College of Allergists, Atlantic City, N. J., June, 1947.

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*Correction.*—Progress in Allergy: Physical Allergy in Dermatology, Stephan Epstein, M.D., F.A.C.A., Annals of Allergy, 6:617-623 (September-October), 1948.

1. Tables 1, 2 and 3 (pages 618-619): 8γ instead of 8/gm.
2. Page 622, Line 7: However, their investigations indicate that this effect is *not* due to the "antihistaminic" action.

# ANNALS *of* ALLERGY

*Published by the  
American College of Allergists*



VOLUME 6

January through December, 1948

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On January first, Dr. Arthur F. Coca will begin the practice of allergic diagnosis as applied in internal medicine and the medical specialties with the pulse-dietary survey.

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From time to time, a theoretical and practical two-week course, covering the subject of idioblaptical allergy, may be offered to groups of six to eight; preferably to physicians who are themselves seriously affected by idioblaptical symptoms.

Arthur F. Coca, M.D., 425 Grant Avenue, Oradell, New Jersey

### FIFTH ANNUAL SESSION OF THE COLLEGE

April 14-17, 1949

Since its inception the College has missed only one annual session as a result of adhering to the request of the United States Government during the height of the war that all conventions which would interfere with the travel of military personnel be avoided.

As the *ANNALS* go to press, John H. Mitchell, M.D., Chairman of the Program Committee, announces that although a large number of papers have been submitted, papers are still receivable subject to the acceptance of the Program Committee. This also includes papers *by title*. Members of the Program Committee—Drs. Harold A. Abramson, Ralph Bowen, L. J. Halpin, and Leon Unger, will meet in Chicago, December 19, with Doctor Mitchell to make final decisions concerning the program. They must have three copies of a 250-word summary (1 page) of each paper. Please send summaries to John H. Mitchell, M.D., 695 Bryden Road, Columbus, Ohio.

Jonathan Forman, M.D., Columbus, Ohio, is director of publicity for this meeting and will have his office in the Exhibition Hall of the Palmer House.

Already there are forty Technical Exhibits of interest to allergists, as well as about twenty Scientific Exhibits. With the Chicago Allergy Society and the Cook County Medical Society invited to attend, a registration of at least 1,000 is expected.

Spring in Chicago is like spring in Paris. Since Sunday, April 17, is Easter Sunday, announcement of church services will be listed in the Program.

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\*Stillians, Arthur W.; Concealment of Cutaneous Blemishes, Arch. Derm. & Syph. 57: 279 (Feb.), 1918

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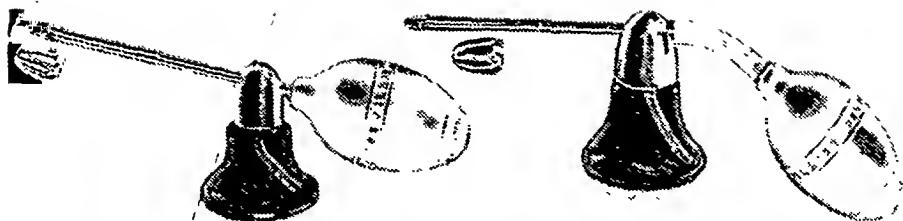
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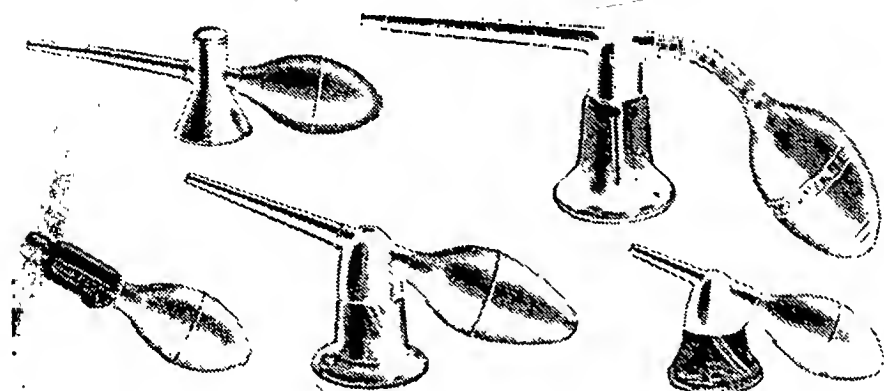
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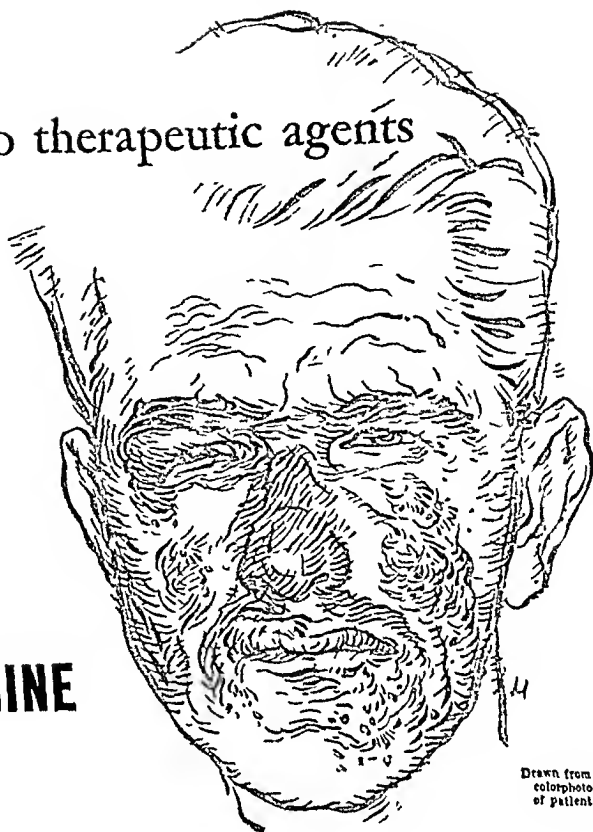
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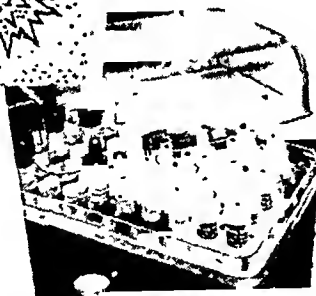
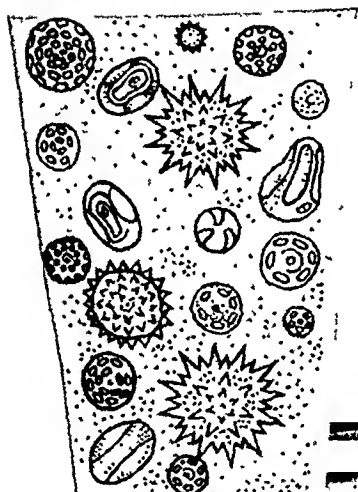
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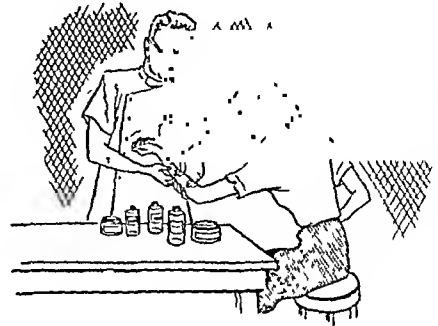
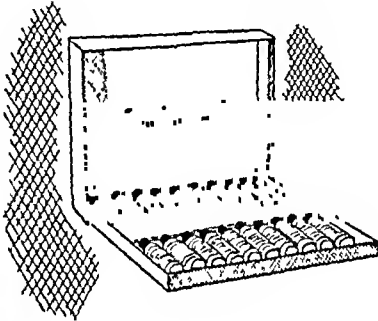




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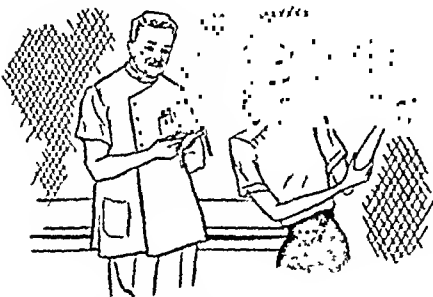
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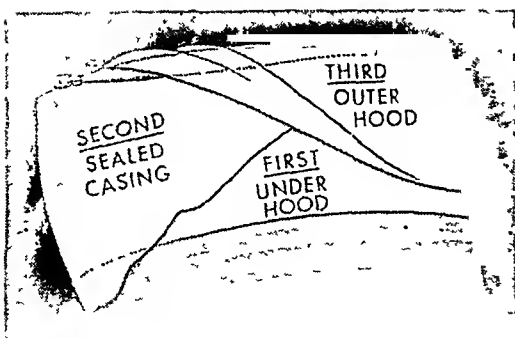
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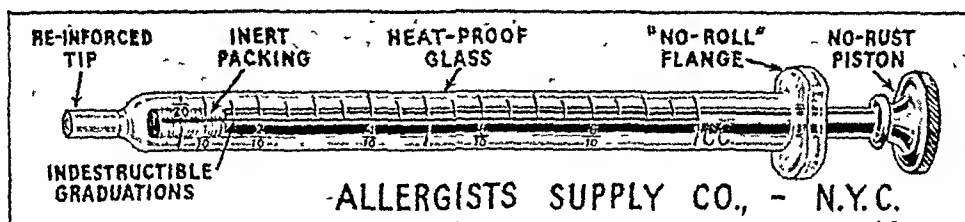
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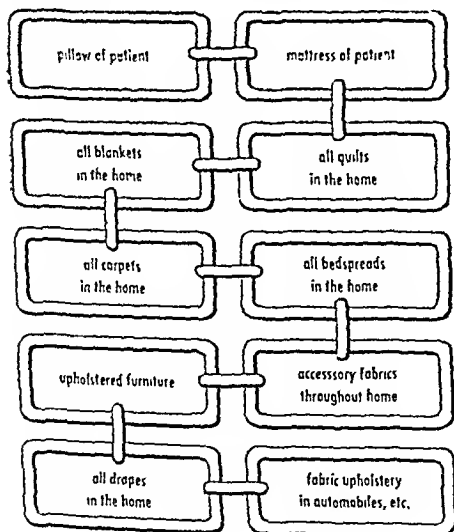
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\*Arthur F. Coca, M.D., F.A.C.A. (honorary)  
Annals of Allergy, Oct.-Nov. 1948

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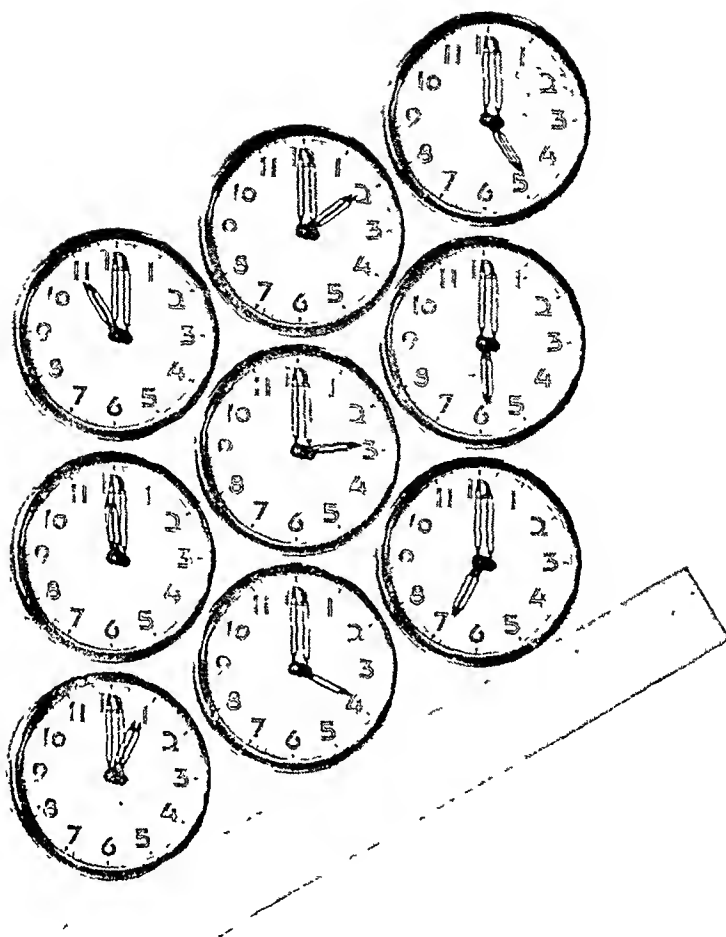
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St. Louis 3, Missouri

Executive Office  
423 La Salle Medical Bldg.  
Minneapolis 2, Minnesota

Annals of Allergy is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, editorials, case reports, new suggestions, news items and matters concerning the affairs of the American College of Allergists.

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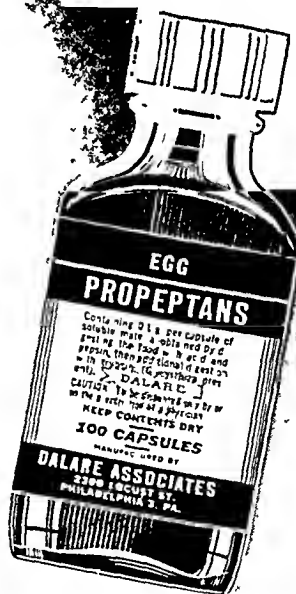
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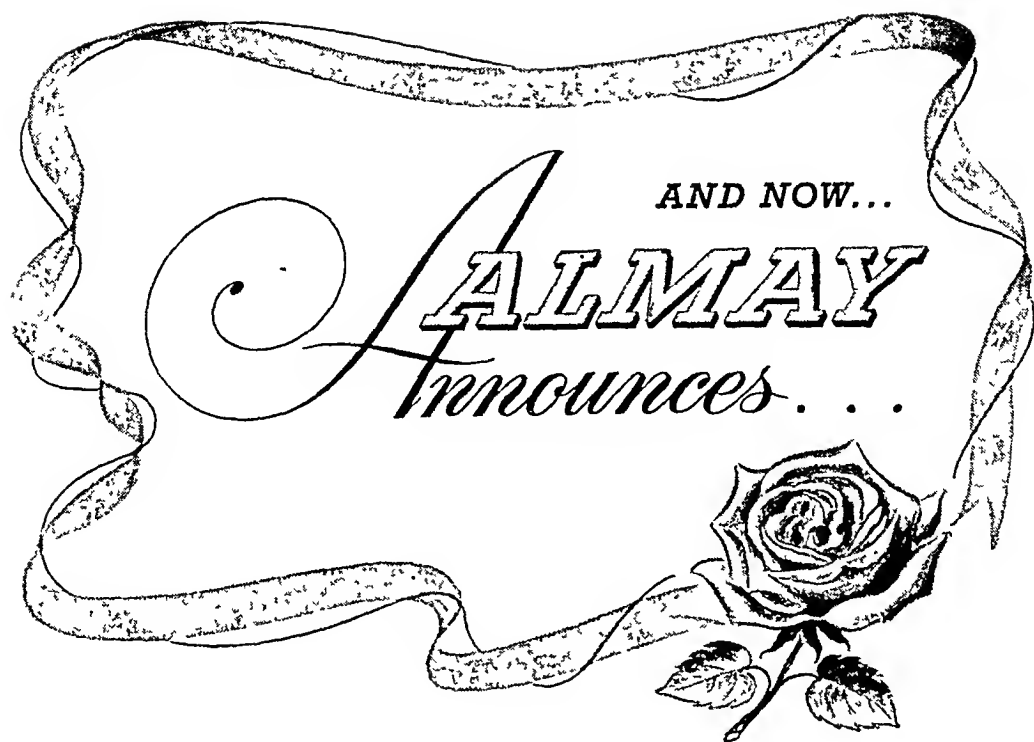
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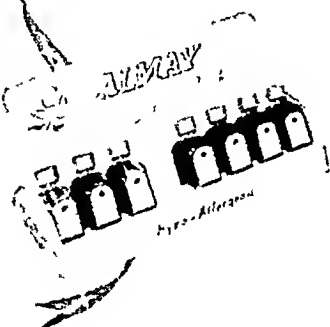
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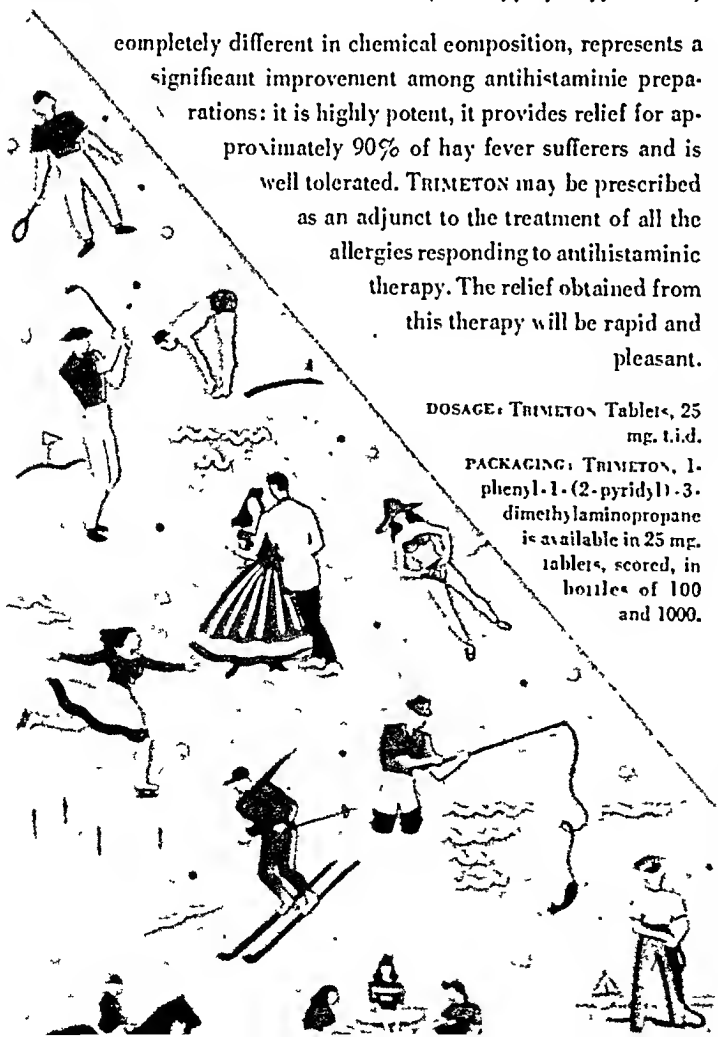
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# ANNALS of ALLERGY

*Published by the  
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Volume 6

September-October, 1948

Number 5

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## DIAGNOSTIC CUTANEOUS REACTIONS TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY AND OF ANTIGEN PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF DIVERSE DISEASES

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THE consistent isolation by special methods of specific types of green-producing or alpha streptococci from infection foci and from tissues involved in various epidemic and non-epidemic diseases has been reported.<sup>5,7</sup> The inherent or acquired property of streptococci to localize and produce lesions in tissue of animals, corresponding to those chiefly involved in the spontaneously occurring disease in question, was often so pronounced as to resemble the specific pharmacological action of certain drugs or chemicals.<sup>3,4</sup> This tendency of streptococci to localize electively was shown to be due to the production, within the organisms themselves and free in broth cultures, of highly labile toxins or poisons which had predilection for, and specific damaging action on, the very tissues in which localization and growth occurred in the spontaneous and experimentally reproduced diseases. Similar original and corroborative studies on specificity of alpha streptococci have been reported by others, to which reference has been made in prior publications.

Evidence of specificity of streptococci as isolated in studies of various diseases was not limited to elective localization. The distribution curves of cataphoretic velocity of the streptococci varied according to the embryologic origin of the tissues chiefly involved and for which the streptococci had respective elective affinity.<sup>6</sup> Moreover, the different types were agglutinated, and extracts were precipitated specifically by the respective antiserums.<sup>5,7</sup>

Each of these procedures used for demonstrating specificity of streptococci—elective localization, agglutination and precipitation reactions, and

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From the Bacteriologic Research Laboratory, Longview Hospital, Cincinnati, Ohio.

Presented at the meeting of the American College of Allergists, Atlantic City, N. J., June 7, 1947.

cataphoretic mobility—are cumbersome, time consuming, and difficult. Special methods for their isolation and for preservation of specificity have been found necessary, and even these do not always suffice. A search, therefore, was made for simpler methods for the detection of the presence of specific types of streptococcal infections and antibody response in persons suffering from different diseases.

In agreement with the erythematous antibody-antigen reaction discovered by Foshay<sup>1</sup> in tularemia and with the antigen-antibody reaction described by Francis<sup>2</sup> in pneumonia, it was found that an immediate erythematous reaction on intradermal injection of streptococcal antibody served for the detection of specific antigen, and that a similar reaction to intradermal injection of antigen served for the detection of specific antibody in skin or blood in persons suffering from the respective type of streptococcal infection. It is the purpose of this paper to describe the methods used and report the results obtained in cutaneous tests made with natural and artificial streptococcal antibody and with antigen, and the effects of therapeutic injection of artificial antibody in persons suffering from diverse diseases associated with, or due to, green-producing or alpha streptococci.

#### METHODS OF STUDY

The streptococci from which natural and artificial antibody and antigen were prepared were isolated chiefly from nasopharyngeal swabbings of persons ill with diverse diseases and, as a control, from well persons remote from epidemics. For the isolation of specific types, serial dilution cultures of the NaCl-solution washings of the swabbings were made at steps of  $10^{-2}$  or  $10^{-4}$  in tall tubes of freshly prepared dextrose brain broth. Pure cultures of the streptococci were obtained from the end point of growth, and these were grown for only one, two, or three culture generations in this medium and then inoculated into large volumes (3,500 ml.) of freshly prepared, warm, 0.2 per cent dextrose broth. All cultures were incubated at  $33^{\circ}$  to  $35^{\circ}$  for only fourteen to twenty hours, and the growth in the large volumes of dextrose broth was harvested in the bowl of a continuous-feed centrifuge. The putty-like growth was removed from the bowl with a sterile spatula and suspended in glycerol, 2 parts, and saturated NaCl-solution, 1 part, so that each ml. of this suspension contained the growth from 500 ml. of broth, or approximately 1,000 billion streptococci. The streptococci in this suspension, owing to the hygroscopic properties of the glycerol, become dehydrated. Some remained viable for a year or two and remained antigenically specific almost indefinitely. The use of the highly favorable medium, dextrose brain broth, which affords a reduced oxygen tension, the short period of growth of the organisms, and the dense suspension were found essential for the primary isolation of specific types of alpha streptococci and for maintaining their specific properties.

Appropriate dilutions of the dense suspension of the streptococci, and not the streptococci grown indefinitely on artificial mediums, were used for

the immunization of horses, for the preparation of artificial antibody and of antigen as used in cutaneous tests and in treatment, for the preparation of vaccines and solutions of specific polysaccharides and extracts for precipitation tests, and for suspensions suitable for agglutination tests.

Ten per cent solutions of the euglobulin-fraction of the serum of horses that had been immunized with the respective streptococci, and the bacteria-free supernatant of NaCl-solution suspensions containing 20 billion streptococci per ml., that had been autoclaved at 17 pounds pressure for ninety-six hours, diluted with equal parts of NaCl-solution containing 0.4 per cent phenol, were used in cutaneous tests for the detection of specific antigen.<sup>8</sup> The supernatant of suspensions containing 10 billion streptococci per ml., which had been heated at 70° C. for one hour, were used for the detection of specific antibody in skin or blood.

The Luer type of syringe of 0.5 ml. capacity, fitted with a 27-gauge needle, was used. Solutions of antibody and antigen considered homologous to the disease at hand in the persons to be tested, together with heterologous and control solutions, were drawn into syringes before beginning the injections. The skin was disinfected lightly with pledgets of absorbent cotton or gauze moistened with 95 per cent alcohol. Approximately 0.03 ml. of the test and control materials were injected in rapid succession, 5 cm. apart in two rows, into the skin of the volar aspect of the forearm, beginning at the bend of the elbow and proceeding towards the wrist.

The maximal area of the rapidly occurring erythema was outlined with pen and washable ink and recorded in square centimeters by superimposing circles of predetermined size on a 4 by 6 inch transparent discarded x-ray film. The solutions of antibody and antigen were kept in small rubber-capped vials, and the syringes containing the test materials were kept upright in test tubes containing enough 95 per cent alcohol to bathe the needle. They were kept in the refrigerator when not in use. The material in the syringes was not wasted after storage, but a few drops were discarded just before use to wash out any alcohol that might have diffused into the lumen of the needle. Solutions of natural and artificial antibody, when kept in the refrigerator, have been found to remain potent for as long as five and three years, respectively.

The reactions varied greatly in intensity and size, and at times were blotchy and irregular in outline. Their significance was always considered in relation to reactions or lack of reactions following injection of suitable control antibody or antigen and usually of NaCl-solution containing 0.2 per cent phenol. The erythema following injection of specific antigen occurred less often than that following injection of antibody, and was usually less intense and more transient than the reaction that followed injection of antibody. The reactions began to fade promptly. Slight edema and erythema were sometimes noted twenty-four hours later at the site of injection of the antigen. The size of reactions were usually checked by two or three observers, and large and small groups of well persons and per-



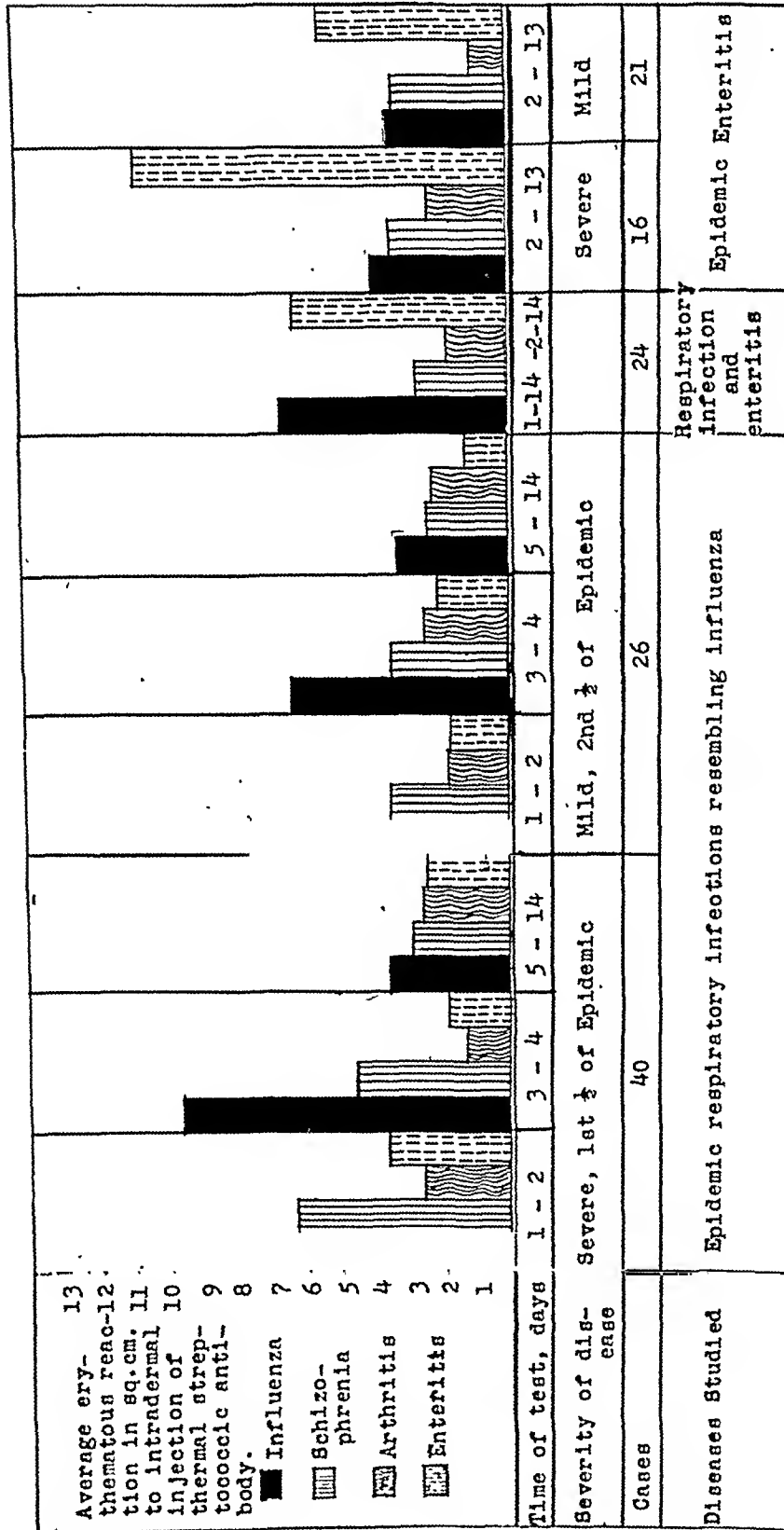


Fig. 1. Erythematous reactions to intradermal injection of thermal antibody produced from alpha streptococci isolated, respectively, in studies of epidemic respiratory infections, schizopneumonia, arthritis, and epidemic enteritis.

# CUTANEOUS REACTIONS—ROSENOW

TABLE I. ERYTHEMATOUS REACTIONS, IN PERSONS SUFFERING FROM INFLUENZA AND OTHER RESPIRATORY INFECTIONS, PERSISTENT HICCUP AND ARTHRITIS, TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE DISEASES

Groups	Reactions of intradermal injection of natural and artificial antibody prepared from streptococci isolated in studies of:						
	Natural Antibody				Artificial Antibody		
	Resp. Infections	Polio-myelitis	Encephalitis	Arthritis	Resp. Infections	Encephalitis	Arthritis
Influenza and other respiratory infections	256 10.42	46 1.76	37 2.2	45 2.3	263 11.04		185 2.13
Influenzal broncho-pneumonia	42 8.90			42 2.90	6 11.14	6 5.46	6 2.43
"Virus" or atypical pneumonia	17 8.3			17 2.05	4 15.17		4 3.12
Epidemic and post-operative persistent hiccup	10 5.12	18 4.10	42 7.38	28 3.12	2 5.13	2 12.32	2 1.76
Neuromyositis and fibrositis		35 3.42	35 5.10	35 9.00		6 4.11	6 9.68
Chronic infectious or rheumatoid arthritis		85 1.50	85 2.60	87 8.12		19 3.47	104 9.63

The figures above the line in each instance indicate the number of persons tested; the figures below the line indicate the average reactions in square centimeters.

sons suffering from different diseases were tested as unknowns. Reactions to several injections of the same test material ran closely parallel. In no instances did persons become sensitized or allergic following repeated intradermal or therapeutic injection of artificial antibody.

Artificial antibody used therapeutically was prepared by autoclaving NaCl-solution suspensions containing 10 billion streptococci per ml., by diluting the respective dense suspensions in glycerol-NaCl-solution 100 fold and autoclaving for three hours after adding 1.5 per cent  $H_2O_2$ .<sup>9</sup> The slightly opalescent solution, containing the sharply agglutinated remnants of the organisms thus obtained, was brought to pH 6.8, diluted 1 to 5 with NaCl-solution, and from 2 to 10 ml. of such dilution were injected subcutaneously or intramuscularly in treatment.

## RESULTS FOLLOWING INTRADERMAL INJECTION OF ANTIBODY

The results following intradermal injection of natural and artificial antibody in persons suffering from influenza and other respiratory infections, influenzal pneumonia, "virus" or atypical pneumonia, epidemic and postoperative persistent hiccup, neuromyositis, and chronic infectious or rheumatoid arthritis, are summarized in Table I. The reactions were highly specific to both natural and artificial antibody.

# CUTANEOUS REACTIONS—ROSENOW

TABLE II. ERYTHEMATOUS REACTIONS, IN PRISONERS AT A PENITENTIARY DURING AN EPIDEMIC OF RESPIRATORY INFECTION, TO INTRADERMAL INJECTION OF ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF RESPIRATORY AND OTHER INFECTIONS

Time of Tests	Persons Tested				Reactions (sq. cm.) to intradermal injection of artificial antibody prepared from streptococci isolated in studies of:					
	Total	Resp. Infections	Number	Per Cent	Chronic Encephalitis	Schizophrenia	Epilepsy	Ulcer of Stomach	Resp. Infections	Arthritis
Dec. 3 to 31, 1946	77	+ 0	14 63	18 82	8.57 13.01	2.82 4.47	1.31 2.00	2.53 4.45	13.57 2.26	1.46 1.55
Jan. 1 to 7, 1947	78	+ 0	46 32	59 41	10.61 10.71	4.46 2.14	1.21 .64	2.35 1.58	10.98 5.02	2.11 1.79
Jan. 8 to 15, 1947	160	+ 0	66 94	41 19	10.96 11.18	5.70 3.56	2.61 1.93	3.10 2.45	12.51 5.73	2.47 2.50
Jan. 16 to Feb. 23, 1947	180	+ 0	6 164	9 91	13.41 10.05	5.77 4.70	2.08 2.60	1.08 3.33	14.18 3.68	2.69 2.05

The results obtained in cutaneous tests made during two institutional epidemics among persons having mild symptoms of schizophrenia, one of respiratory infection and one of enteritis, are summarized graphically in Figure 1. The reactions to the respective artificial antibodies were remarkably specific, roughly proportional to the severity of the diseases in question, and became greatly less as recovery occurred. Pronounced reactions occurred to the two respective homologous antibodies, one prepared from streptococci isolated in studies of respiratory infection and one from streptococci isolated in studies of epidemic enteritis in persons who suffered from both respiratory infection and enteritis.

The results obtained at a penitentiary in prisoners during a sharp epidemic of respiratory infection are summarized in Table II. Each of four groups of persons, who were having respiratory infection when tested, reacted strongly to artificial antibody prepared from streptococci isolated in previous studies of respiratory infection, averaging 13.57, 10.98, 12.51, and 14.18 sq. cm. respectively. Two of four comparable groups that were free from symptoms of respiratory infection reacted significantly greater to the respiratory streptococcal antibody at the height of the epidemic (5.02 and 5.73 sq. cm.) than did two otherwise comparable groups before and after the height of the epidemic (2.26 and 3.68 sq. cm.). This increase during the height of the epidemic, indicating the carrier state, was apparently not due to contact infection.

The abnormally marked average reactions of this and a much larger number of prisoners to artificial antibody prepared from "neurotropic" streptococci isolated in studies of chronic encephalitis, schizophrenia, and from incorrigible prisoners, will be reported elsewhere. Suffice it to state here that intercurrent epidemic respiratory infections did not change the cutaneous reactivity to intradermal injection of two specimens of artificial antibody prepared from "neurotropic" streptococci.

# CUTANEOUS REACTIONS—ROSENOW

TABLE III. ERYTHEMATOUS REACTIONS, IN PERSONS SUFFERING FROM POLIOMYELITIS, ENCEPHALITIS, MULTIPLE SCLEROSIS OR FROM ULCER OF THE STOMACH, TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE DISEASES

Groups	Reactions to intradermal injection of natural and artificial antibody prepared from streptococci isolated in studies of:										
	Natural Antibody					Artificial Antibody					
	Polio- mye- litis	En- ceph- alitis	Ar- thri- tis	Resp. Infection	Ulcer of Stom- ach	Polio- mye- litis	En- ceph- alitis	Ar- thri- tis	Ulcer of Stom- ach	Well Per- sons	Multiple Scler- osis
Acute epidemic poliomyelitis	484 8.97	268 3.30	270 2.41	53 3.21		254 14.21	15 4.21	23 2.45		254 3.09	
Poliomyelitis Contacts	337 4.35	90 1.80	304 1.26	124 1.73		277 7.40				277 2.60	
Well non-contacts in epidemic zones	437 3.64	110 1.30	86 2.46	229 2.07		188 6.81				188 1.62	
Well persons remote from poliomyelitis, encephalitis and influenza	787 1.27	325 0.77	270 1.48	340 2.23		128 1.80		201 1.85		128 0.89	
Epidemic encephalitis	54 3.27	138 6.88	59 1.80	91 3.06			25 9.23	20 2.21			
Multiple sclerosis	9 5.84	9 10.34	9 2.54	9 1.48		14 5.16	14 7.24	14 2.88			14 14.16
Ulcer of stomach or duodenum	39 4.0	39 5.0	39 4.0		39 11.0	13 0.83	13 8.17	13 0.90	13 9.38		13 1.23

The figures above the line in each instance indicate the number of persons tested; the figures below the line indicate the average reaction in square centimeters.

The cutaneous reaction obtained following intradermal injection of natural and artificial antibody in persons suffering from epidemic poliomyelitis and encephalitis, from multiple sclerosis or ulcer of the stomach, and in well contacts and noncontacts in epidemic zones of poliomyelitis and in well persons remote from epidemics, are summarized in Table III. The average reactions to both natural and artificial antibody were uniformly much greater in persons suffering from the disease in studies of which the streptococcus was isolated and from which the reacting antibody was prepared. Moreover, the reactions in well persons to antibody prepared from streptococci isolated in studies of poliomyelitis were proportional to the degree of exposure to poliomyelitis in epidemic zones and were minimal or absent in well persons remote from poliomyelitis.

The average cutaneous reactions obtained in persons suffering from idiopathic epilepsy, schizophrenia, chronic infectious arthritis, involutional psychosis, and dementia paralytica, tested in parallel with natural and

# CUTANEOUS REACTIONS—ROSENOW

TABLE IV. ERYTHEMATOUS REACTIONS, IN PERSONS SUFFERING FROM DISEASES OF THE NERVOUS SYSTEM OR FROM ARTHRITIS, TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE OR RELATED DISEASES

Groups	Persons Tested	Reactions (sq. cm.) to intradermal injections of natural and artificial antibody prepared from streptococci isolated in studies of:					
		Natural Antibody			Artificial Antibody		
		Epi- lepsy	Schizo- phrenia	Arthri- tis	Epi- lepsy	Schizo- phrenia	Arthri- tis
Idiopathic Epilepsy	77	8.27	3.42	2.10	9.60	5.21	2.50
Schizophrenia	89	3.51	5.66	1.42	1.42	7.53	1.93
Chronic infectious arthritis	8	2.89	2.48	6.06	2.06	1.18	4.74
Involuntional psychosis	7	2.11	3.44	2.10	2.74	5.45	1.47
Dementia Paralytica:							
Without Convulsions	24	2.18	1.82	0.87	1.90	1.75	0.89
With convulsions	6	5.79	2.45	1.35	6.87	3.65	2.29

artificial antibody, are summarized in Table IV. A consistently high degree of specificity was obtained with both types of antibody, including a strikingly greater average reaction to antibody prepared from streptococci isolated in studies of epilepsy in persons suffering from dementia paralytica having convulsions, than occurred in persons having dementia paralytica without convulsions. The reactions were uniformly minimal to all antibodies in the uncomplicated group of dementia paralytica, and to heterologous antibody in the groups which reacted specifically to the homologous antibody. Moreover, cross reactions were relatively greater in persons suffering from epilepsy or schizophrenia to both types of antibody prepared, respectively, from the more closely related streptococci isolated in studies of epilepsy and schizophrenia, than to antibody prepared from the streptococci isolated in studies of arthritis.

## RESULTS FOLLOWING THERAPEUTIC INJECTION OF ARTIFICIAL ANTIBODY

The presence of abundant specific antigen and minimal specific antibody in skin or blood of persons in the early stages of respiratory infections, the gradual diminution of antigen, and the increase of antibody with time during the natural course of the disease and as recovery ensued, are shown graphically in Figure 2.

The effects of therapeutic injection of artificial antibody on the antigen and antibody content of skin or blood in persons suffering from influenza or other respiratory infections are shown graphically in Figure 3. The decrease in specific antigen, as shown by intradermal injection of artificial antibody prepared from streptococci isolated in studies of influenza and other respiratory infections, and the increase in antibody, as shown on intradermal injection of the corresponding antigen following therapeutic injection of specific artificial antibody, were greater in twelve and six hours, respectively, than occurred in six to nine or more days during

# CUTANEOUS REACTIONS—ROSENOW

the natural course of the disease (Fig. 2). There was usually a corresponding improvement in symptoms, especially in the early stages of the disease as antigen was sharply reduced and antibody abruptly increased.

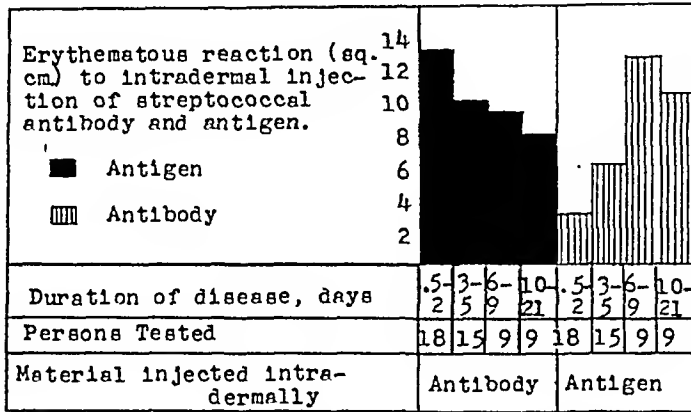


Fig. 2. Erythematous reactions, in persons suffering from epidemic respiratory infections, to intradermal injection of antibody and antigen prepared *in vitro* from streptococci isolated in studies of respiratory infections, according to the duration of the disease.

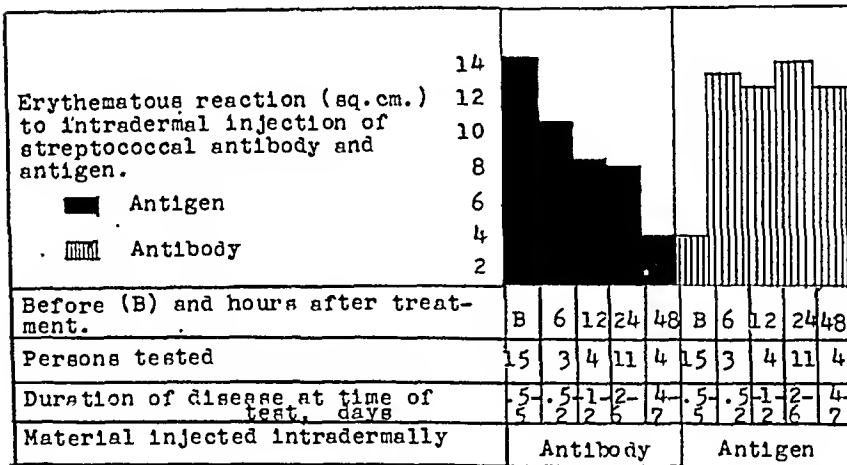


Fig. 3. Erythematous reactions, in persons suffering from influenza or other respiratory infections, to intradermal injection of antibody and antigen prepared *in vitro* from streptococci isolated in studies of epidemic respiratory infections, before and after therapeutic injection of homologous streptococcal antibody.

The effects of therapeutic injection of artificial antibody prepared from streptococci isolated in studies of poliomyelitis on the content of specific antigen and antibody in the skin or blood of persons suffering from epidemic poliomyelitis, are summarized graphically in Figure 4. A striking reduction in antigen and an increase in antibody occurred in three hours and persisted for forty-eight hours following one therapeutic injection per

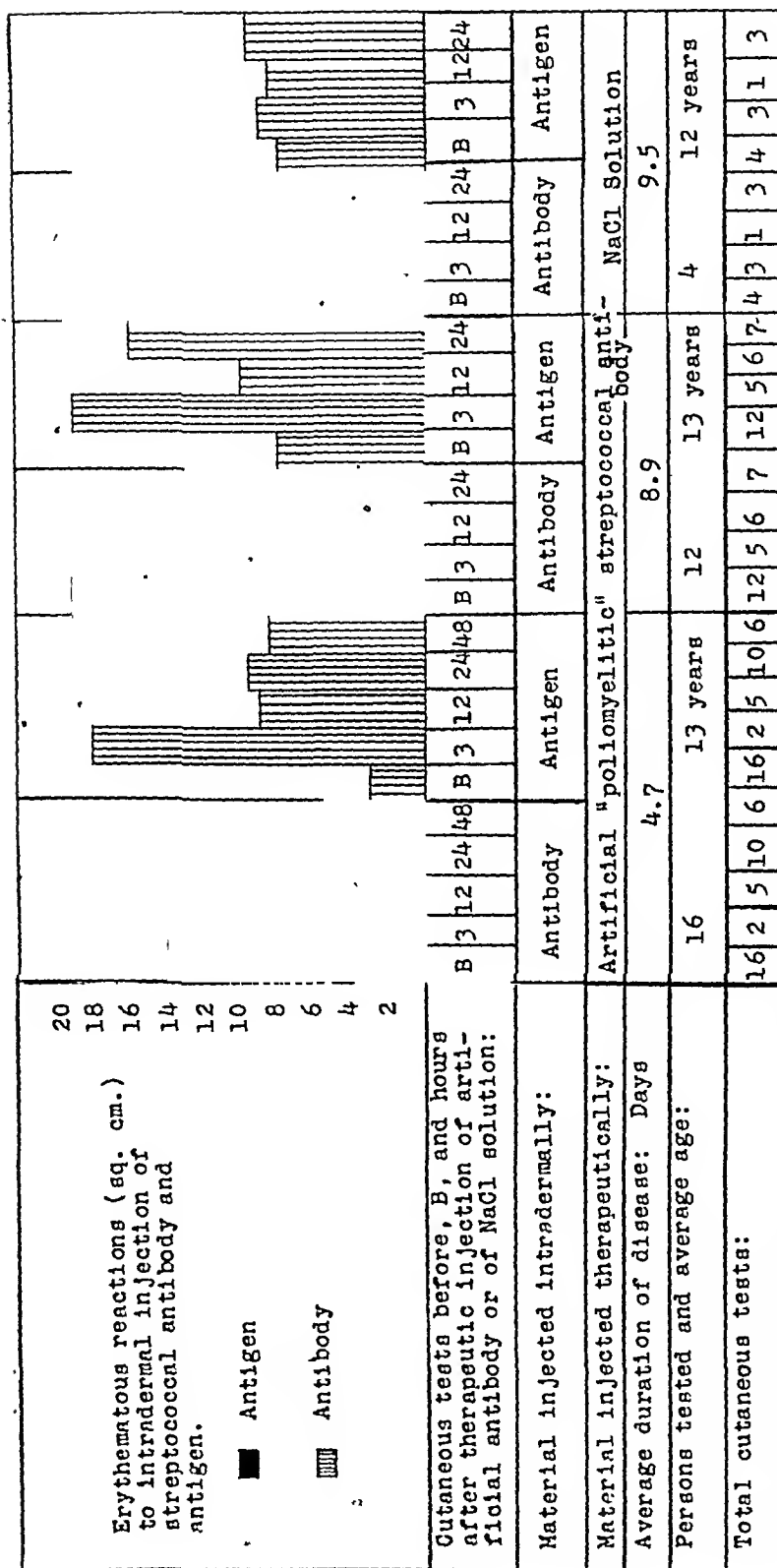


Fig. 4. Erythematous reactions, in persons suffering from epidemic poliomyelitis, to intradermal injection of antibody and antigen prepared from streptococci isolated in studies of poliomyelitis, according to the duration of the disease and therapeutic intramuscular injection of artificial antibody.

person of antibody in the group of sixteen persons in the early stages of the disease. A moderate decrease in antigen and increase in antibody occurred in the group of twelve persons in the later stages of the disease, and no change in antigen and antibody occurred in the four control persons having poliomyelitis who received "therapeutic" injections of NaCl-solution.

#### COMMENTS AND SUMMARY

The results of cutaneous tests in persons suffering from widely different epidemic and nonepidemic diseases, made with natural and artificial antibody and with antigen prepared from green-producing or alpha streptococci isolated in studies of persons suffering from the respective diseases and of well controls remote from epidemics, are reported.

The reactions to intradermal injection of natural antibody prepared in horses and artificial antibody prepared *in vitro* with the respective streptococci, indicating specific antigen in skin or blood and, hence, corresponding specific types of streptococcal infections, ran closely parallel. The reactions were usually proportional to the severity of respective symptoms, fairly constant in chronic disease, greatest in the early stages of acute disease, and gradually became less pronounced and finally disappeared after recovery.

Reactions to intradermal injection of antigen, indicating specific antibody in skin or blood, were often slight or absent at the onset of acute respiratory infections and epidemic poliomyelitis, but gradually increased in size as recovery occurred, and then disappeared usually as antigen also disappeared.

There was a great difference in the length of time that specific antigen was demonstrable in skin or blood in the natural course of different acute diseases. The reaction indicating specific streptococcal antigen, in acute respiratory infections followed by a transient immunity, usually disappeared in two weeks, whereas in epidemic poliomyelitis, followed by an enduring immunity, the reaction usually persisted for six or eight weeks. The erythematous reactions are not considered diagnostic of disease but rather diagnostic of the presence in skin or blood of respective specific streptococcal antigen and antibody and, hence, of specific types of streptococcal infections.

The reactions obtained on intradermal injection of natural and artificial streptococcal antibody or of antigen are almost certainly not allergic or urticarial in character, nor are they due to histamine. Wheal and pseudopodia formation and itching, characteristic of allergic and histaminic reactions, almost never occurred.

Reactions to antibody in persons suffering from the different diseases, and who reacted most strongly to homologous antibody, were relatively greater to antibody prepared from streptococci isolated from persons suffering from more closely related diseases than to antibody prepared from



streptococci isolated from persons suffering from more distantly related diseases. Reactions in persons ill with various diseases were minimal to antibody prepared from streptococci isolated from well persons remote from epidemics. Moreover, reactions in well persons and persons ill with noninfectious diseases remote from epidemics were slight or entirely negative. Reactions to control NaCl-solution, to which 0.2 per cent phenol had been added after autoclaving, were slight or negative alike in ill and well persons.

Therapeutic injection of natural, and especially of artificial, antibody caused a greater reduction in antigen and a great increase in antibody in the course of hours than occurred in the natural course of acute disease during several to many days. With striking reduction of antigen and increase of antibody following therapeutic injection of artificial antibody, there was usually a corresponding clinical improvement and, in the very early stages of respiratory infection and poliomyelitis, abrupt disappearance of symptoms.

The cutaneous tests which have been developed and reported herewith are considered of importance because they are strictly objective, easily performed and controlled, and because the information obtained is in such strict accord with the demonstration, by animal inoculation, serologic and cataphoretic methods, of the presence of specific types of alpha streptococci in the diseases studied.

The supernatant solutions are designated as artificial or thermal antibody because they were prepared *in vitro* and because they agglutinated the respective streptococci in high dilution, hastened the destruction of streptococci on intraperitoneal injection in animals, caused a prompt reduction in antigen and increase in antibody on therapeutic injection, and had apparent curative action in the treatment of persons suffering from streptococcal infections homologous to the streptococcus from which the antibody injected was prepared.

Acknowledgment of the co-operation of the many attending physicians and nurses, of hospital superintendents and health officers, which made these studies possible, is hereby made.

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## TRIMETON IN THE TREATMENT OF ALLERGIC DISEASES

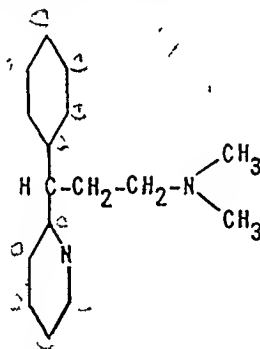
F. W. WITTICH, M.D., F.A.C.A.  
Minneapolis, Minnesota

HAVING given a clinical trial to practically all of the antihistaminic agents since Benadryl was first introduced, we undertook the past year clinical observations with Trimeton to determine whether it had certain advantages over antihistaminic agents previously introduced. With the report of this small series, it is obvious that for statistical purposes it is inadequate. However, a close personal study was made of each of these cases, and the patient was told that the drug was prescribed to give symptomatic relief.

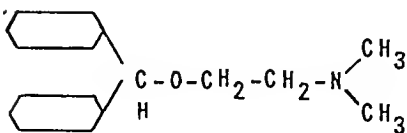
Trimeton was employed as an adjunct in allergic management and the majority were receiving concomitant immunization measures. The agent was administered only to those where allergic management proved inadequate or where insufficient time had elapsed before the pollen season to adequately control symptoms.

Although Trimeton was distributed to a considerable larger number of patients, only 125 could be properly tabulated for various reasons. An attempt was made to exclude those who exhibited evidence of secondary infection. The ages of the patients ranged from eight to seventy-four years.

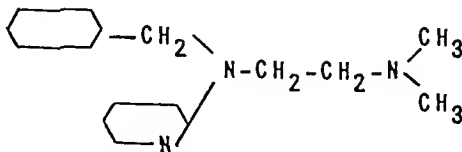
Trimeton (brand of Prophenpyridamine) has the empiric formula  $C_{16}H_{20}N_2$ , molecular weight 240, with a structural formula as shown below.



It is insoluble in water but soluble in organic solvents and in dilute acids such as hydrochloric acid, forming the hydrochloride. The relationship of Trimeton with Benadryl and Pyribenzamine is shown in the respective structural formulae:



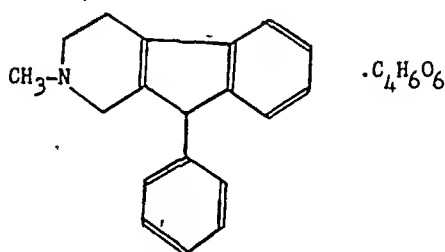
BENADRYL



PYRIBENZAMINE

Trimeton-1 phenyl-1 (2-pyridyl)-3 dimethylaminopropane was supplied through the courtesy of the Schering Corporation, Bloomfield, New Jersey.

Thephorin belongs to a different class of compounds and has a structural formula as follows:



Thephorin

When comparing the antagonistic action against the toxic effects characteristic of histamine in animals, Trimeton showed greater activity with equal dosage. Incidentally, Trimeton shows antispasmodic activity, as measured by its ability to produce relaxation in isolated rabbit gut which has been induced into spasm by barium chloride or by carbamylcholine. The comparison of the antihistaminic action of Trimeton, Benadryl, and Pyribenzamine is quoted by Brown.<sup>2</sup>

Trimeton is available in 25 mg. tablets, scored. It was found that this dose three times daily was usually sufficient for the average adult, and that one-quarter to one-half a tablet would suffice for children according to age. The action of the compound commences in fifteen minutes to one hour and lasts four to six hours. Conclusions were based on questioning the patient within one or two days following the onset of treatment. Instructions were given to take the drug only when symptoms presented themselves.

At the onset, difficulty was encountered when comparing the reports of patients who had previously taken other antihistaminic agents. Syndromes which were considered allergic only were treated in this series.

Of the 125 patients which were tabulated, eighty-nine of them manifested respiratory allergy in some form, and of the eighty-nine, thirty-three were cases of pollenosis, eighteen were perennial nonseasonal allergic rhinitis, twenty-nine were bronchial asthma, four of whom had exacerbations during the pollinating season, and nine cases had a mixed syndrome of asthma and hay fever. Of the 125 patients, thirteen of them had simple urticaria, and one had angioneurotic edema. Of this series there were four with gastrointestinal allergy. There were seven cases of allergic headaches, including migraine. Six patients had atopic dermatitis, and two had contact dermatitis. Two patients of the series had general pruritus, and one patient had Ménière's disease.

Results were classified as "good," "fair," and "poor." The patients with good results had complete, or almost complete freedom from symptoms. Those with fair or moderate relief were those whose results were con-

sidered satisfactory in the majority of patients, and those with poor results were those who obtained no relief whatsoever.

Of the thirty-three patients with pollenosis, twenty-five had good results, six had fair results, and two had no results at all. The total improved, therefore, of the pollenosis group was about 90 per cent.

Of the eighteen patients with perennial allergic rhinitis, five obtained good results, four were fair, and nine obtained no relief.

Of the total of thirty-eight asthmatics, nine of whom had asthma and hay fever, six obtained good results, four obtained fair results, and twenty-eight showed poor results.

Of the thirteen patients with simple urticaria, six obtained good results, three had fair results, and four showed poor results.

One case of angioneurotic edema showed good results, although during her attack she was also taking vitamin K. This patient is still on Trimeton and with no recurrence, although recurrent attacks have been fairly frequent.

Of the four patients with gastrointestinal allergy, one obtained moderate relief from cramps, but the others obtained no relief.

Of the seven cases of allergic headaches, including migraine, six with moderately severe and very severe symptoms showed relief to date, but the time has been too brief to determine how many will show permanent relief. One patient obtained no relief.

Of the six cases of atopic dermatitis, the symptomatic relief of the pruritus was good in three, fair in two, and poor in one.

Of the two patients with contact dermatitis, no relief was obtained.

Of the two patients with general pruritus, one achieved good results, and one had fair results.

One patient with Ménière's disease obtained fair results with relief of the tinnitus and considerable relief of the vertigo. By taking 25 mg. of Trimeton three times a day, the patient could avoid this syndrome when subsequently exposed to the offending agent, tobacco.

*Side Effects.*—One patient with a perennial allergic rhinitis complained of nausea, which disappeared on withdrawal of the agent and recurred upon resuming treatment. One patient developed abdominal pains and vertigo. Another patient with severe hay fever over a period of several years, who had not received any immunization measures, obtained good relief until the height of the hay fever season, when she developed asthma for the first time. Whether this can be attributed to a shift in the sensitized or "shock organ" remains to be determined.

#### SUMMARY

When comparing the results of Trimeton with the previous observations from the older antihistaminic agents, it has been shown to give temporary symptomatic relief, particularly in patients suffering from pollenosis.

Ninety per cent of the hay fever cases due to pollen obtained good or fair relief with no side reactions. This slightly exceeds the percentages of the older antihistaminic agents such as Pyribenzamine, as reported by Arbesman and his co-workers,<sup>1</sup> and Feinberg and Friedlander.<sup>3</sup>

Comparing the results of Trimeton with those of Waldbott<sup>5</sup> for Neohetramine for perennial allergic rhinitis, hay fever, and urticaria, they were favorable, if not superior. According to Frank's observations<sup>4</sup> for Thephorin, a greater percentage of his nonseasonal rhinitis and urticaria cases were benefited; although when compared with our observations of Trimeton, a greater percentage of our pollenosis cases were benefited. Side effects, when compared with the other antihistaminic agents studied, were comparatively rare, which is a distinct advantage. Side effects, however, must be expected in varying degrees from any of the antihistaminic agents so far introduced.

The most beneficial effects were obtained when used in conjunction with immunization measures and when preventing systemic reactions with high dosage of pollen or the inhalant extracts by administering a 25 mg. tablet about a half-hour before the antigen injection. This procedure would allow increasing the maximum dose of the antigen within tolerance, than when taking the pollen extracts alone.

Trimeton is a valuable adjunct in proper allergic management. Its greatest value is in the treatment of pollen hay fever and hives, and it appears somewhat superior in the small series observed.

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## ENVIRONMENTAL EXCITANTS OF IDIOBLAPTIC ALLERGY (INHALANTS)

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THE subject of this report has received some consideration in the earlier publications upon idioblapsis, especially in the paper entitled "Sensitivity to Cigarette Smoke"<sup>1</sup> and in a short section of the second edition of my monograph<sup>2</sup> (p. 55).

The environmental air-borne excitants of idioblaptic allergy have been found to cause important symptoms (epileptic seizures, hypertension and others); they sometimes interfere seriously with the interpretations of the pulse-dietary record, and they are often difficult to identify, sometimes even eluding the search for them entirely. These facts, together with the recently increased occurrence of illustrative cases in my experience, have made the publication of the latter seem worth while.

### CASE REPORTS

*Case 1.*—The case of A. F. C. has been difficult and instructive, because of the number of the inhalant allergens that affect him, the variety and seriousness of his allergic symptoms and the length of time that was needed—on account of the continual exposure to some of the inhalants—to identify all of his food allergens. Perhaps the clinical material obtained from the long observation of this patient can be most usefully analyzed with reference to his most important symptom: allergic ("essential") hypertension.

Throughout most of his life this man had suffered severe allergic symptoms (migraine, heartburn—sometimes incapacitating—dizziness, tormenting extra systoles and others), but previous to the age of sixty-six his systolic blood pressure had usually ranged between 108 and 112. At about sixty-six and one-half years of age, December, 1941, a maximal pressure of 134/88 followed the ingestion of potato, and promptly after avoidance of the potato the pressure fell to a minimum of 100/70. Soon after he had submitted, in May, 1942, to sympathectomy (right side only) he abandoned all dietary restrictions for a short time, and two months after the operation a pressure of 154/84 was recorded. In November, 1943, the pressure stood once at 190/106. The highest systolic pressure observed in this patient has been 202, the highest diastolic 122. In 1944 after the main food allergens had been identified and eliminated from his diet, his average pressure through sixteen days (one test daily) was 137/74.7, (highest systolic 158, highest diastolic 80). He does not smoke and his sensitivity to tobacco smoke was first observed by accident after a long drive with a cigar smoker in a closed automobile. At one and one-half, three and one-fourth and four and one-half hours after the exposure the diastolic pressure readings were 96, 90 and 100, as compared with 74 and 78 on the two previous days and 86 and 78 on the two following days. After the exposure and before the next meal there was also anorexia and near-nausea. No food allergen came in question.

In 1945, notwithstanding avoidance of the major food allergens and efforts to avoid tobacco smoke, the hypertension advanced. Table 1 shows the pressure recorded practically daily between August 18 and September 18, 1945. The average 147.6/91.6 is higher than it had been in the previous year. In the spring of 1946 house dust became suspect, and dust-proof covers were placed on all bedding

# IDIOLAPTIC ALLERGY—COCA

TABLE I. BLOOD PRESSURE OF PATIENT A.F.C. TAKEN DAILY FROM AUGUST 18 TO SEPTEMBER 18, 1945. AVERAGE 147.6/91.6

140/90	150/90	150/90	150/94	150/96	146/90	150/96
150/92	144/96	150/94	148/90	130/96	144/96	158/98
150/90	152/96	150/90	152/94	152/90	152/96	144/88
152/96	148/86	140/80	142/84	140/86	140/86	160/96
150/96	140/88					

Gas range moved to semidetached kitchen October 5, 1945.

TABLE II. BLOOD PRESSURE OF PATIENT A.F.C. TAKEN ALMOST DAILY FROM MARCH 29 TO APRIL 29, 1946. AVERAGE 161/89

148/86	168/94	148/84	164/86	164/84	174/96
160/90	170/98	156/84	158/86	162/84	152/78
162/90	178/96	158/86	158/90	160/88	184/90
152/86	144/86	162/90	146/82	170/96	160/90
162/86	166/98	158/94	160/90		

Dust-proofing March 28, 1946

and most of the upholstered furniture. Nevertheless, the pressure increased somewhat, averaging 161/89 (Table II). At that time milk and cereal had not yet been recognized as residual allergens, but exposure to suspected kitchen range gas had been greatly minimized by building a semidetached kitchen. In the fall of 1946 after the cereals had been eliminated and the patient had been proved to be nonsensitive to pea, bean, peanut and onion, and having tried to lessen the exposure to dust by having him for the greater part live and sleep in the partly closed-off sun porch, the average pressure was found definitely lower in the period November 5 to December 10 (Table III).

It was not possible to judge how much of this improvement was due to elimination of the food allergens and how much to the modest measure of dust avoidance, but a prolonged stay (half-hour or more) in the house was regularly followed at once by chest oppression and dry mouth, and on the day following the periodic vacuum cleaning there was often diarrhea. It was these recurring sequences that led me at last to investigate the existing devices for the clearing of dust from the air of human habitations. There were three different types of these, all of which are efficient for their several special purposes.

The first is the familiar filter-box designed for installation in a window during the pollen seasons for the purpose of drawing pollen-free air into the room, and, through the positive air pressure thus maintained, preventing to some extent the entry of pollen-laden air through other avenues. The other two devices are much more expensive.

One of these is a system of ducts carrying air to and from the different rooms and passing it under pressure through "fiber-glas" filters and generally through water, these being connected with the central heating body.

The third device consists essentially of a set of electrically charged plates upon which are deposited practically all dust particles that are in the air passing over them. The instrument may be placed in any convenient situation in living or sleeping rooms.

It seemed to me that for my purpose a fourth type of instrument should be satisfactory and might be manufactured at a cost within the means of most persons needing it. Essentially the device consists of two "fiber-glas" filters set close together in slots in a metal housing in front of an exhaust-fan. The fan should deliver about 1,000 cubic feet of filtered air per minute. The instrument is easily portable.

When such a filter was set in motion, January 8, 1947, in the living room of A.F.C., his blood pressure in the sun porch stood at 154/90. Two hours later the odor of the lubricating oil was noticeable in the bathroom on the floor above, indicating effective circulation of the filtered air through the house. From that time the patient has lived continually in the house. The forty-eight blood pressure

# HIOBLAPTIC ALLERGY—COCA

TABLE III. BLOOD PRESSURES OF PATIENT A.F.C. TAKEN ALMOST DAILY FROM NOVEMBER 5 TO DECEMBER 10, 1946. AVERAGE 149/81.7

152/94	166/94	144/82	170/91	161/68	126/72
163/94	142/73	118/80	138/70	150/60	140/80
153/91	150/88	146/74	148/72	140/80	140/76
144/80	144/72	134/80	150/70	170/90	150/84
160/84	160/86	160/82	146/80	140/70	141/80

Stopped eating molasses, November 2, and stopped eating all cereals November 3. Living on soup only.

TABLE IV. BLOOD PRESSURE OF PATIENT A.F.C. TAKEN AT SEVERAL DAY INTERVALS FROM JANUARY 9 TO MAY 15, 1947. AVERAGE 142.5/76

140/78	132/74	142/83	127/72	140/74	142/74	140/72	142/76
144/78	131/79	142/76	130/76	148/76	132/68	138/69	150/76
141/76	140/79	146/74	150/70	151/82	160/62	146/74	134/74
150/72	136/69	140/70	150/78	140/70	150/72	144/80	138/78
136/70	134/88	136/82	142/74	138/70	147/66	132/74	146/60
136/72	144/82	137/78	140/82	140/70	128/68	136/78	132/68

Air filter started January 8, 1947. Living in house from January 8, 1947.

readings observed from January 9 to May 15, 1947, are shown in Table IV. These readings include all those taken after exposure to tobacco smoke, unavoidable dust and other inhalants.

House dust causes other allergic symptoms in this patient. Continuous sneezing and tearing of long standing ceased so it after the air filter began to function, and have recurred only upon occasional later exposures to dust. Chest oppression and diarrhea have been mentioned. Neuralgic pain is an uncommon symptom, although it regularly follows exposure to paint fumes and cement dust.

A practically experimental clinical test of the patient's nonreaginic sensitivity to dust was made on January 30, 1947. At 8:30, one hour after an allergenic meal, with the pulse at 72, he stood for twenty minutes before the functioning filter. The fan had throughout the preceding three weeks been sucking air through the filters from the front; and the electrician had just reversed the motor so that it was now blowing the air through the filters from behind, which favored a loosening of the recently deposited dust from the anterior surface of the front filter. At 8:50 the patient noticed chest discomfort, and his pulse had increased to 78 (filter was stopped). At 9:00 the chest discomfort was marked; there were extrasystoles, and the pulse stood at 82. At 9:10 the pulse was 74, and at 9:40 it had dropped to 60 and the chest discomfort had diminished. The expected diarrhea occurred on the following day. The somewhat elevated systolic pressure of 150 observed at 10:00 is not significant because the pressure had not been measured previous to the test.

*Case 2.*—In the past year I have had opportunity to study three hypertensive patients none of whom were found nonreaginically allergic to any food. As in the similar instances with other symptomatology, avoidance of such common nondietary excitants as tobacco, perfumed cosmetics, soaps, dentrifices and the like, and soap powders was advised.

One of the three patients refused to complicate his living with such restrictions and withdrew. The other two observed the precautions and also covered mattresses and pillow cushions, et cetera, with dust-proof covers. The systolic pressure on one of these (A.H.) had never been below 260 under the observation of her physician, Dr. John Dickson of Bogota, New Jersey, and at her first two visits to my office it registered above 300. The diastolic pressure was 130 and 120, respectively; Dr. Dickson had found it about 130. She had had a slight cerebral hemorrhage in July, 1945.

The first week of the pulse-dietary survey with a varied diet had revealed no food that caused a distinct and specific tachycardia. However, the variations of the maximal daily rate 70 to 78 indicated some allergenic influences. Moreover, it was noted that the before-rising count was usually higher than the retiring count.



# IDIOBLAPTIC ALLERGY—COCA

After the dust-proofing of the bedding on April 11 the pulse-rate before rising was always slower than before retiring.

April	5	6	7	8	9	10	11*	12	13	14	15	16	17	18
Before rising	—	68	64	72	68	66	64	56	62	56	62	64	54	60
Retiring	—	60	—	68	64	56	60	58	72	68	66	62	64	70

\*Dust-proof covers on bedding.

On May 4 the blood pressure stood at 194/118, and at that time the patient was urged to obtain an air filter. Another sign of the favorable effect of the dust precautions was the fact that the daily maximal pulse rate on each of the previous twelve days (excepting two days when it was 68) had been 70. On the date of this writing (August 29, 1947) the patient reports that she has still been unable to obtain the needed air filter, but she expects to do so soon. She reports, "I feel much better than I did previous to the dust-proofing of my bedding." No examination of her blood pressure has been made since May 4, 1947.

*Case 3.*—The third case, A. B., also a patient of Dr. Dickson, is a man of fifty-seven whose blood pressure had been constantly 180/100 or higher and had stood at 220/116 on his first visit to my office. He had had several "attacks of fainting" in which he fell. His eyes were regularly "blood-shot" on rising in the morning. He had had urticaria, indigestion, neuralgia and occasional abnormal tiredness, constipation, and headaches. He feels better in the summertime.

From the beginning of the pulse-dietary course, the pulse generally ranged from 72 to 84, with an occasional 86 or 88 having no relation to the diet. On the third, fourth and fifth days the retiring and before-rising counts were:

March	24	25	26
Before rising	82	80	80
Retiring	76	72	78

This record indicated a moderate acceleration of the pulse due to an inhalant allergen originating in the bedding, and dust-proof covers were ordered and were put on the bed on the eighth day. The before-rising pulse counts on the subsequent six days were, 72, 72, 74, 72, 70, 68. These were always lower than the preceding retiring counts, 80, 78, 80, 78, 78, 82.

The blood pressure taken on the day following the covering of the bedding was 160/110. One month later it was 166/106, and an experimental air filter was installed. At that time two uncovered mattresses were discovered in the living room and were ordered into the attic. Two weeks later the pressure stood at 140/92. Since that time there have been intermittent exposures to paint fumes, rotenone, and commercial fertilizers, sometimes with accompanying mild tachycardia (up to 88) and increased blood pressure. His blood pressure readings in July, 1947, were:

1—148/72†	6—159/92	10—162/86	19—142/82	28—150/92
4—168/82	8—158/92	15—166/90	21—162/98	29—168/86

†At beach all day.

On July 26, the pressure at 9:00 a.m. was 164/94. After he had worked in the garden all day with rotenone and commercial fertilizer, the pressure was taken by two observers with two instruments with the following results:

Observer A with instrument B	178/102
Observer B with instrument B	180/104
Ten minutes later:	
Observer B with instrument A	190/98
Observer B with instrument B	190/98

The patient is pleased with his much improved general well-being and freedom from the minor symptoms mentioned above. While it seems possible under ideal environmental conditions to reduce the hypertension in this case much further,

## IDIOLAPTIC ALLERGY—COCA

any such effort might be economically prohibitive and would almost certainly not be undertaken by the patient in his present satisfactory state of health. Although in all of the foregoing case reports the environmental allergic excitant has been spoken of as "house dust," the question of its exact identity has not been raised. The omission was deliberate; all efforts to solve this mystery have failed. For the practical purpose of avoidance, however, it is sufficient to know that that objective can be attained by dust-proofing plus air filtration.

Similarly, in the following case the environmental excitant was not exactly identified, but its source could be determined and avoided. The chief complaint of this patient was a dermatitis. In view of the notorious pitfalls of dermatological diagnosis and my own inconsiderable experience in it, I shall content myself with a description of the lesions in the case.

*Case 4.*—Patient L. M. P., aged sixty-one, was referred on May 9, 1946, by Dr. H. E. Bejack, New York, N. Y., with a history of "allergic dermatitis" unimproved by various treatments over a period of about two months.

The patient presented a scaly, itching eruption of forearms, thighs (inner surfaces) and back of neck (skin thickened) with angioneurotic swelling of cheeks and eyelids. The pulse ranged at first from 54 to 97. The pulse-accelerating allergens were found to be cereals, orange (itch), honey (itch), fowl, lamb, a popular shaving cream (pulse 108), soap (exposure to soap powder caused itching and prolonged acceleration of the pulse). Almay shaving cream caused no reaction.

Within three weeks after beginning the pulse-dietary course, the eruption was healing everywhere and the angioneurotic edema had disappeared. The normal pulse range averages 50 to 63 but slight contact with some inhalant allergens probably continues, raising the rate occasionally to 66 or 68. All lesions finally disappeared, leaving only a negligible perineal pruritus. The pretreatment blood pressure taken by Dr. Bejack at about weekly intervals was 130/70, 115/85, 115/85 and 120/85. In my office May 10, it was 140/85. The pressure after treatment has been 122/66, 110/64, 110/70 (Dr. B.), and 120/70. No skin tests were done. The patient has remained entirely well (latest blood pressure 112/66) throughout the succeeding seven months. There was no local or other medication.

It is worthy of note that whereas soap powder as an air-borne inhalant allergen caused both tachycardia and exacerbation of the dermatitis, the same soap in bar form could be used by the patient without either of those consequences.

### CONCLUSIONS

1. Allergic (essential) hypertension has been shown to be caused, not infrequently, by air-borne specific excitants, sometimes in subjects who are not allergic to any foods in their diet.
2. Extensive dust-proofing of bedding and upholstered furniture did not provide adequate protection against house dust in the three cases cited. A portable air filter is described with which the desired result was obtained in the two cases for which it was used.
3. One instance is cited in which an air-borne allergen (soap powder) could be reasonably suspected as specific excitant of "allergic dermatitis" (neurodermite?).

NOTE: This study is continued and concluded in the succeeding paper on Dust-Seal.

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## DUST-SEAL

### Its Use in the Avoidance of "House Dust" by Dust-Sensitive Persons

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IN a previous publication<sup>3</sup> a few instances of nonreaginic sensitivity to that mysterious inhalant allergen known to allergists as "house dust" were described, in which the dust-proofing of bedding and upholstered furniture alone markedly lessened the patients' symptoms. However, the circumstances in one of these (A.F.C.) indicated a continuing, if lessened, exposure to dust, the effects of which were serious enough to suggest the installation in the house of a fiber-glas air filter for the removal of dust originating elsewhere than in the bedding and upholstery.

The clinical result of this measure was highly gratifying; the average blood pressure was reduced from 149/81.7 to 142.5/76, and the patient was free from chest pain, conjunctivitis, and gastrointestinal disturbance—this in spite of his living in the house, whereas he had previously been obliged to live in the partly closed-off sunporch.

There remained the inconvenience of his having to shun the house during the several hours following the periodic vacuuming, while the filter was running for the removal of the scattered dust particles which had escaped the cleaner. On some occasions it was necessary for the patient to be in the house during this operation or too soon afterward. These happenings were regularly followed by immediate chest discomfort and by diarrhea on the next morning, and these frequently recurring sequences suggested that allergenic "dust" may originate also in the floor coverings.

It was at this juncture in November 1947, that I had a conversation with Mr. Leonard S. Green,\* concerning the remarkable properties of a product of this organization in the reduction of the bacterial content of the air in enclosed rooms and the consequent lessening of infections in the personnel occupying them.

Mr. Green has kindly contributed the following summary of information concerning this matter.

"Effective means for controlling the bacterial-dust phase of air contamination, in an endeavor to minimize the acute respiratory infections among all personnel in test areas, were first studied by Van den Ende and Andrewes<sup>6,7</sup> in England and later by the U. S. Army and Navy. The best procedure was determined to be the use of absorptive oils as a means of choking off secondary reservoirs. This might take the form of depositing an oil imperceptibly on floors or in fabrics, or both, depending upon

Dust-Seal is the trade name of a product of L. S. Green Associates.

\*President of L. S. Green Associates, Air Sanitation Products, 160 West 59th Street, New York 19, N. Y.

the environment. A hospital, for instance, on account of the volume of textiles used, can take full advantage of the new practice.

"No bactericidal action is claimed or contemplated in the application of modern oiling methods. The absorption and retention obtained, however, is quite high. Dr. Henry Wise, former member of the Commission on Air-Borne Infections, reports that the reduction in the number of bacteria which could be liberated from a treated blanket amounts to 75 to 95 per cent as compared to an untreated blanket exposed for the same period of time under similar surroundings. These foreign particles (bacteria, dust) can be easily removed with soap and water in a normal washing operation; but wool has the peculiar property of retaining a large portion of the recommended oils after *water washing*, so that very little re-introduction of the oil is necessary. However, the oil would be completely removed with dry cleaning. Cottons behave differently; a larger portion of the oil is removed by water washing and, therefore, a larger portion must be put back. The above-mentioned determination of retentivity was made with the suction of a vacuum cleaner and by dropping steel balls on contaminated blankets over exposed Petri dishes.

"Working in barracks and hospital wards under conditions of adequate control, the investigators report reductions in bacterial counts (taking them both by plates and Folin bubbler samplers) of 50 to 90 per cent. This improvement in air purity was accompanied by fewer hospital admissions at Camp Carson, Colorado,<sup>5</sup> than in the group used for control (5,750 men in both areas). In this project not only floors, the oiling of which reduced bacterial dispersion by 70 per cent during hours of maximal activity, but also blankets, mattress covers, sheets and pillow cases were treated. The impregnation of the fabrics alone added another 10% to the bacterial reduction.

"The investigators in England, working in barracks with individuals subject to outside exposures, established an infection rate of 7 per 1,000 in test groups of 1,300 to 1,700 men, as against 38 per 1,000 in the control group, or a difference of about 80 per cent.<sup>1</sup> As yet no similar data in degree of performance have been developed or published in this country.

"Impressed by the apparent efficacy of a microbic glue, to be used as a part of good housekeeping practice, this firm was organized to determine the type of oiling compound needed for civilian environments. The oils used for coating barrack floors were found to be impracticable, since both walk-quality and appearance had to be considered along with labor costs in application.

"The first formula used was an oil mixture, which is easily emulsifiable in water. When the milk-white, odorless emulsion is sprayed or sprinkled to thorough soaking upon rugs or carpets or upholstered furniture, it quickly becomes quite invisible. Since the oil is nonvolatile, the fabric is not made more than usually inflammable.

"The emulsion is quickly prepared, as follows: A suitable pot is filled

about two-thirds full (one quart) with warm water from the faucet; place four or five heaping tablespoonfuls of the commercially distributed cream on the surface of the water and emulsify (two to three minutes) with an egg-beater. Make up with water to one gallon and distribute with fine-holed garden watering pot. For effective treatment, rugs and carpets must be thoroughly soaked. Such treatment has not caused noticeable injury to even fine Chinese and Turkish rugs."<sup>†</sup>

#### CASE REPORTS

*Case 1.*—The first person with nonreaginic dust sensitivity in whom the protective action of Dust-Seal could be observed was patient A.F.C. This case was most favorable for the purpose of the particular experiment, because of the easily observable, one may even say measurable, consequences of his exposure to dust, which have been described in a previous report.<sup>3</sup>

Dust-Seal was first applied by the patient to the rugs with a "flit-gun" on two successive days. This amounted to a mere surface dampening of the rugs that produced no encouraging change in the average blood pressure. Two months later, on January 15, 1948, all the rugs were thoroughly soaked with the emulsion.

In the period from January 19 through March 25, the recorded blood pressures were:

<i>Systolic</i>	<i>Diastolic</i>	<i>Systolic</i>	<i>Diastolic</i>	<i>Systolic</i>	<i>Diastolic</i>
122	72	138	74	130	70
132	78	146	68	130	78
130	72	146	70	130	76
136	78	130	78	146	76
136	72	146	80	142	70
126	72	132	68	124	70
138	80				

The average of these readings is 134.5/74.

This reduction of the blood pressure becomes the more significant of a diminished exposure to dust, as a result of the immobilizing effect of Dust-Seal, when the fact is considered that since the Dust-Sealing the use of the air-filter has been entirely discontinued. Moreover, the patient remains in the house while the vacuum cleaner is in operation without experiencing the slightest symptom of his dust-sensitivity.

*Case 2.*—Patient A.B. has been described also in the previous report.<sup>3</sup> This man's systolic pressure, which had been constantly 180 or higher, had dropped to an average of 158.3 after the dust-proofing of his bedding and upholstered furniture and the installation of a fiber-glas air filter. He was not food-allergic.

On March 5, 1948, the heavy carpeting of the patient's bungalow was thoroughly soaked with the Dust-Seal emulsion under the personal direction of Mr. Green. The average of the previous twenty readings of the patient's systolic pressure was 160 (range 148 to 170). From March 16 to March 25, the daily systolic pressure readings average 143 (range 140 to 148, with one reading of 158).

*Case 3.*—V.H.S. suffered with chronic rhinitis, canker sores, headaches, nervousness and abnormal tiredness. Skin tests showed her to be dust-sensitive; her husband and son had also been found skin-test-positive to dust. However, she has a nonreaginic sensitivity to dust, which is seen in a pulse rate of 102 observed "after making beds." Her normal pulse ranges from 64 to 80. No nonreaginic food sensitivities have been discovered. The patient reported some improvement of her symptoms after replacing her down pillows with air-filled ones.

In March, 1948, she applied dust-proof covers to mattresses, pillows and cushions and wore a dampened mask while dusting and making beds. "This seemed to

<sup>†</sup> For more details concerning the treatment of various fabrics with Dust-Seal, see the manufacturer's special literature.

# DUST-SEAL—COCA

TABLE I. PULSE RECORD OF V. H. S. IN MARCH AFTER APPLICATION OF DUST-PROOF COVERS, AND IN MAY AFTER APPLICATION OF DUST-SEAL

	March				May			
	27	28	29	30	19	22	25	27
Before rising	60	60	62	60	—	—	—	—
Breakfast	76	78	80	78	80	82	76	—
	80	90	90	82	76	76	80	—
	90	80	90	84	76	72	74	66
	80	78	—	80	—	—	—	—
Cleaning, making beds	90	98	100	90	76	76	70	80
	—	92	84	—	No mask used	.....	70	70
Lunch	76	76	76	—	—	—	—	—
	84	80	82	—	82	78	—	78
	80	84	78	—	80	74	—	80
	—	74	—	—	76	74	—	74
Mid P.M.	—	80	—	—	78	—	74	72
	—	74	—	—	—	—	—	—
	—	74	—	—	—	—	—	—
Dinner	—	74	78	76	—	—	—	—
	—	82	80	74	72	74	80	74
	—	80	80	74	74	72	78	78
	—	74	76	74	72	72	76	74

— indicates no record made.

help a great deal," symptomatically, though the pulse remained generally high and erratic.

Dust-Seal was liberally applied to floor covers about April 20, and a few weeks later "blankets and slip covers were washed and rinsed in the emulsion."

The pulse record of V.H.S. in Table I shows the effect of the Dust-Seal on the pulse rate. It is noteworthy that the high rates in March always occurred in the morning, the period of greatest exposure to dust.\*\*

In June the patient wrote, "I am delighted about the improvement of my husband and son—they are both allergic to house dust by skin test, having a hay-fever condition most of the winter. Three times, I have noticed an improvement. First, when I eliminated down pillows and quilts. Second, when I covered the mattresses. Third, when I used the Dust-Seal." As for her own chronic rhinitis, she writes it is "better than it has been for a year."

*Case 4.*—M. M., aged thirty-nine, had bronchial asthma with chronic rhinitis. She had consulted an allergist who found her skin-test-positive to feathers and cheese; she had received a series of injections. Consulting me on August 31, 1946, she reported that she had suffered a severe attack of asthma over several days at the time of her August period (a coincidence that recurred in the next two months). The pulse in these attacks was high (in the nineties from a normal low of about 60). The October attack culminated in an alarming status, making it imperative to all concerned to decide upon the most probable cause of the "attacks" and take appropriate action.

The usual dust and feather precautions had been instituted; there were no food allergens in the diet, and the cutaneous tests to ragweed pollen, as well as to grasses and oak, were quite negative. Inhalation of vaporized ragweed pollen extract caused no asthmatic symptom. The most likely cause of the attacks seemed to be an "internal allergen" appearing at the periods. The patient has two children, and she and her husband agreed to artificial menopause with a series of x-ray treatments, which were administered.

Two further periods were experienced, both accompanied with milder asthmatic attacks and pulse rates up to about 104. Thereafter there were no periods nor frank asthmatic attacks.

However, the chronic rhinitis with mild wheezing continued, and the cause of

\*\*It is also noteworthy in this connection that in the investigation at Camp Carson mentioned in Mr. Green's summary, "the bacterial content of the air during the bedmaking was 1200 per cent greater than during a quiet period in the same ward with the same occupancy."

these symptoms was believed to be house dust, the scratch-test for which caused a  $\frac{3}{8}$ -inch wheal with a two-inch flare.

Installation of a fiber-glas air filter caused no noticeable relief of these symptoms, but they ceased shortly after the thorough Dust-Sealing of the floor coverings on February 15, 1948. Previous to that time the patient had had some symptomatic relief with the use of an "iodide prescription" obtained from another physician. She has not used this since. Five months have passed with no recurrence of any of her symptoms.

*Case 5.*—G. M., the four-year-old son of the foregoing patient, had had occasional asthmatic attacks previous to the institution of the dust precautions (cutaneous tests have not been done). There was no asthma thereafter, but whenever he played with his teddybear, pushing his nose deep into the fur, he had continuing spells of sneezing.\* Recently his parents dipped the teddybear into a pot of Dust-Seal emulsion and dried it. Thereafter the boy played with the thing as intimately as before but without ever sneezing.

*Case 6.*—Mrs. McC., aged twenty-four, had the following symptoms: abnormal tiredness, headaches, indigestion, asthma, chronic rhinitis, dizziness, urticaria, angio-neurotic edema. Her most alarming symptom was spells of partial blindness, the nature of which was not determined because she has never been competently examined in an attack. The pulse survey failed, and resort was had to conservative sympathectomy after a successful survey following two ganglion blocks by Dr. E. A. Rovenstine. Since then the patient has experienced only one attack of blindness, which followed shortly after the eating of egg, to which food she is still sensitive.

Her nonreaginic sensitivity to dust was indicated by the observation that her pulse was regularly higher before rising in the morning than it was just before retiring. Bed-mattresses and pillows were dust-proof covered, and there were no heavy rugs on her apartment floors. Nevertheless, there was still some dizziness, tiredness, very slight "headachy" feeling and a melancholic depression which was more marked at the periods. Finally the one large piece of furniture, an antique divan, came under suspicion as a possible source of allergenic dust. Into this divan one and a half gallons of Dust-Seal emulsion were poured, and the piece was dried out under a warm sun.

Immediately after this operation and in the succeeding three months, the patient was quite free from the listed symptoms, experiencing only some irritability at the periods.

The evidence for the effectiveness of Dust-Seal in this case is of questionable value, because it is lacking in real objectivity, resting to only a limited degree upon the husband's positive assertion and involving the more interesting question, whether the several "psychoneurotic" symptoms can actually be caused by an inhaled allergen.

#### DISCUSSION

The experiences here described mark the product Dust-Seal as an efficient, economical, harmless and easily applied immobilizer of allergenic dust in fabrics in which that allergen is presumably generated.

In the cited cases the Dust-Sealing was applied to sources of the allergen which are not closed off by the familiar dust-proofing. However, there seems to be no reason why mattress fillers and also upholstery stuffing cannot be Dust-Sealed, without appreciably increased cost.

*(Continued on Page 517)*

# REACTIONS TO HISTAMINE IONTOPHORESIS IN THE THERAPY OF MULTIPLE SCLEROSIS

## Preliminary Report

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THE search in recent years for a theory which would explain the origin of multiple sclerosis has led to a proposal that the disease may be connected with an allergic reaction to the products of the patient's own central nervous system, or to allergic phenomena connected with bacterial infection. Thus, at the fourth annual session of the American College of Allergists there were presented papers<sup>11,12,14,15,17</sup> dealing with the theory, origin, and the therapy of multiple sclerosis with these specific aspects.

The work of Horton and co-workers<sup>5,12,16</sup> stimulated the writer to explore the possibility of developing a therapeutic technique of administering histamine by iontophoresis rather than by the intravenous route, for several reasons: (1) the veins need not be punctured; (2) the apparatus is inexpensive; (3) hospitalization is not required; (4) sterile equipment need not be employed; (5) the dose of the drug administered can be readily controlled by concentration, current density, time and electrode area; (6) histamine administered iontophoretically forms depots in the skin;<sup>1,4,5,6</sup> (7) it is adapted for home use, and the technique can be easily carried out either by the patient alone or with the help of the family.

The therapeutic principles of Brickner and Franklin<sup>8,9,10</sup> were used as a guide in therapy.

### METHOD

In general, the previous technique described by the writer<sup>2,3</sup> for the iontophoresis of epinephrine in asthma was employed, with certain modifications required for histamine. Only one lead of the equipment was used, although it is possible to treat three separate areas of the skin, either in succession or simultaneously. Canton flannel, 3 inches wide and 12 inches long, was folded twice over lengthwise, so that the final area was approximately 12 square inches (3 inches by 4 inches). This was applied to the anterior aspect of the forearm with the required concentration (up to 1 per cent) of histamine acid phosphate\* solution, and contact was made with an electrode of aluminum foil which was held by a rubber pad and strap against a flat copper positive plate. Current up to 8 milliamperes with this area has been employed, although not more than 5 milliamperes have been recommended for home therapy. The current

The author is indebted to Mrs. Erna Teige for assistance in the research program.  
\*Ergamine, kindly supplied by Burroughs-Wellcome.



density, therefore, has generally not exceeded  $\frac{2}{3}$  of a milliamperere per square inch. This current density may be exceeded, but it is believed that no change should be made until further investigations have been made on the patient's general reactions and blood pressure.

The blood pressure, pulse rate, oscillometric index and temperature were followed, as well as the subjective response of the patients. The patient was told to expect a flush and possibly throbbing of the blood vessels in the head. This relieved most of the anxiety connected with the first experience of the flush. In general, the length of each treatment was fifteen minutes, with the concentration of the solution increased in three steps from 0.25 to 1 per cent, with the current increased from 2 to 8 milliamperes, depending upon the reaction of the patient. Oscillometric readings were obtained in the upper part of the arm and forearm. Certain patients complained of abdominal discomfort, which was probably due to the liberation of gastric juice. An antacid mixture of glycine, three parts, calcium carbonate, seven parts, was routinely administered in the form of tablets†, two before and two after therapy. Further details of the investigative and therapeutic plan will be presented in the brief descriptions of cases studied during the past year.

Eleven cases have been treated during the past year, details of which will appear in a subsequent publication. In order to enable others to follow the procedure, the following cases (Nos. 4 and 10 in the series) are presented.

#### CASE REPORTS

*Case 1.*—J. S. was a thirty-six-year-old married woman with two children. She had had multiple sclerosis for approximately four years. Two years before she was seen by the author, she improved slightly following a course of intravenous histamine. She had much difficulty in walking when she was first seen by the writer and was unable to use the subway or go shopping. Treatment was begun on July 12, 1948, with 0.25 per cent histamine solution, the current being 2 milliamperes for fourteen minutes. With this dosage the primary flush appeared at about seven minutes. The relationship of the blood pressure to the dose of histamine and the onset of the flush is given in Table I. Note that with increased dosage the flush usually begins earlier and the drop in blood pressure is, in general, more noticeable. The oscillometric index was essentially unchanged. The plan of initiating therapy, prior to permitting home therapy, is well brought out in Table I, which should be consulted for details. It is of importance that this patient took approximately 100 milligrams of niacin daily during the time of, and simultaneously with, her histamine therapy, and that she was able to take two treatments per day without immediate untoward effects. Shortly after beginning therapy the patient seemed much better and was not as much fatigued on walking about. She was able to use the subway and to go shopping alone. She stated, "My legs don't jerk as much from the joints." Her vision was much improved. At present she has been placed on home therapy.

It might be argued that the improvement in this patient may be due to factors other than those connected with the administration of histamine. For example, niacin,

† Intralac, kindly supplied by Schenley Laboratories.

# MULTIPLE SCLEROSIS—ABRAMSON

TABLE I. BLOOD PRESSURE, DOSAGE PLAN AND FLUSHES: CASE 1  
The Patient Received Equipment for Home Therapy

Date	Before mm. Hg	After mm. Hg	Dose Histamine as the Acid Phosphate	Primary Flush After Therapy Began Approximateyl (Minutes)
7/12	118/84	115/84	0.25% 3 ma. 15 min.	7
7/13	120/84	115/70	0.5% 2 ma. 15 min.	7
7/14	118/88	118/72	0.5% 3 ma. 15 min.	6
7/15	115/88	102/70	0.5% 3 ma. 15 min.	7
7/16	115/84	112/60	10 pellets (2.75 mg.) 3.5 ma. 20 min.	10
7/17	118/82	115/68	0.5% 4 ma. 15 min.	10
7/19 a.m.	115/78	112/70	1% 3.5 ma. 15 min.	5
7/19 p.m.	115/78	115/60	1% 4.5 ma. 15 min.	5
7/20 a.m.	112/70	100/56	1% 4.5 ma. 15 min.	6
7/20 p.m.	110/78	110/60	1% 3.5 ma. 15 min.	6

was taken simultaneously. It was quite possible that this striking improvement was due to a synergism between histamine and niacin. Dr. R. M. Brickner, who was kind enough to refer this patient for therapy, informed the writer that, in his opinion, the improvement was not a spontaneous remission but was probably due to the pharmacologic action of the histamine. Further data, of course, must be obtained, and the future history of the patient under this type of therapy must determine whether or not the therapeutic technique is responsible for the clinical results.

*Case 2.*—E. W. was a twenty-five-year-old married woman who had had multiple sclerosis for five years. Her first symptom occurred when she collapsed in the street, three months after her marriage, and could not move her legs. She was able to walk afterwards, but poorly. The diagnosis of multiple sclerosis was made at that time. She had had two previous series of treatments with histamine intravenously, without any improvement. The iontophoretic treatment was begun with 1 per cent histamine acid phosphate solution administered for ten minutes, with a current of  $3\frac{1}{2}$  milliamperes. The blood pressure was 96/60 before her first treatment and dropped to 84/48 at end of therapy. She felt slight dizziness after therapy but was able to walk readily. She stated at the time that she felt that "hope was gone." The next day her dosage was increased to  $4\frac{1}{2}$  milliamperes for fifteen minutes. She then mentioned that she had been frightened by an intern whom she had overheard saying that he would rather have a brain tumor than multiple sclerosis. Since that time she had been exceedingly depressed. Four hours later on the same day the patient took a second treatment. The blood pressure at the beginning of this second treatment was 100/68 and at the end was 84/54. During this treatment there appeared sudden movements of the joints of the arms and legs. The patient received successive treatments on the two following days and then a fifth treatment four days later. At this time the patient felt that there was no improvement. She stated that she had had

histamine before with no improvement and there was no improvement this time either. She felt, however, that in spite of the rather severe reactions that she had, she was not any worse. During the treatment on July 26, 1948, the left leg jerked during the flush and there was twitching of the left side of the face. The sixth treatment was given on July 28. The patient remarked that she was frightened about her multiple sclerosis. On July 29 the patient said that she had had a secondary flush following her treatment of the previous day, and mentioned that she believed that the histamine had damaged her heart. On coming to the office that morning she had sensations of a tight feeling in the throat and of choking.

This case is representative of an instance in which the patient states that no improvement occurs during therapy, and ostensibly is in direct contrast to the previous case described. However, this patient walked seventeen blocks by herself following the ninth treatment. It is evident that she has a severe anxiety neurosis as well as multiple sclerosis. In addition, she has been subjected to many traumatic situations incidental to her disease, all of which makes it difficult for either the doctor or herself to evaluate the results of therapy. She is planning to continue the therapy at home, after a suitable number of treatments have been administered under medical supervision.

#### DISCUSSION

There are nine other cases under therapy (as this report is written), all of whom show, to a certain extent, better muscular co-ordination, better ocular co-ordination, or both.

The therapy of multiple sclerosis by histamine is not a desensitization to an allergic reaction. Indeed, the use of histamine iontophoretically in ordinary allergic reactions, such as those occurring in the bronchial tree, is contraindicated here, because in all likelihood asthmatic attacks would be produced. It is recognized that small doses of histamine have been used to desensitize the patient to various allergic syndromes. However, the pharmacologic effect of histamine, as administered by Horton and his co-workers and as administered here, is dependent upon the maintenance of vasodilatation by a pharmacologic reaction.

Our present purpose is to give the patient at least ten office visits, before a galvanic machine is recommended for the use of the patient at home. The following memorandum is given to the patient:

#### *Directions to Patients for the Self-Administration of Histamine in the Therapy of Multiple Sclerosis*

1. Attach the electrodes to the iontophoresis machine, making certain that the red plug matches the red socket. This is the positive pole. The negative pole is the inert reference electrode and can be placed anywhere on the body or as demonstrated to you in the doctor's office. The positive pole may be placed in the anterior aspect of the forearm. If you decide to use another location of your body, please come to the office so that your reaction to that site may be tested, since absorption varies in different parts of the body. The rate of the absorption from the site must be predictable. For example, if the histamine is administered in the thigh the absorption of the histamine will be accelerated.
2. Obtain a piece of cotton flannel, 12 inches long and 3 inches wide, and fold over as directed. Have a sheet of aluminum foil ready for the positive pole of the galvanic machine.

## MULTIPLE SCLEROSIS—ABRAMSON

3. Dissolve 1 gram of histamine acid phosphate (Ergamine Phosphate—Burroughs-Wellcome) in 100 c.c. of distilled water. If distilled water is not available, tap water may be used temporarily. Measure 10 c.c., or approximately  $2\frac{1}{2}$  teaspoonfuls, of this solution, using a plastic measuring spoon, and spread uniformly on the dry Canton flannel. Keep the remaining solution in the refrigerator.

4. Place the canton flannel, wet with the solution, on the anterior aspects of the forearm; place the negative reference electrode on the designated place, making certain that there are no cuts or pimples under the electrode area. If metal touches the skin, or if there are bruises or pimples, there will be a concentration of electricity in that area and an intense burn will be felt. All jewelry should, therefore, be removed. Otherwise, the reaction, as you know, is simply itching with slight irritation.

5. After the electrodes are firmly in place, make certain that the rheostat is down to zero and turn the current on. Slowly increase the current. If burning occurs, make certain that the electrodes are uniformly in contact with the skin and that there are no breaks in the skin. Increase the current slowly to 5 milliamperes. This should not be exceeded before discussion with the doctor.

6. Maintain this current for fifteen minutes, or as otherwise directed.

7. If fainting occurs, an injection of  $\frac{1}{2}$  c.c. of epinephrine 1:1000 will instantly relieve the symptoms due to the histamine.

8. Keep the following record of each treatment:

Name .....

Time, beginning of treatment: .....

Time, completion of treatment: .....

Total time: .....

Flush appeared after .....minutes.

Current of.....milliamperes.

General reaction after therapy: (Include occurrence of secondary flushes).

It is believed that prolonged iontophoretic therapy with histamine combined with vasodilatation by mouth (e.g., Niacin) provides a greatly simplified form of therapy with therapeutic possibilities equivalent to intravenous therapy. It may also prove effective in other degenerative diseases of the central nervous system, as well as in obliterative vascular disease.

### SUMMARY

The successful therapy of multiple sclerosis by the intravenous administration of histamine has led to the development of an iontophoretic technique of administering histamine in this disease. The use of the electric field to introduce histamine into the human skin has certain advantages: (1) the veins need not be punctured for prolonged periods of time; (2) the apparatus is inexpensive; (3) hospitalization is not required; (4) sterile equipment need not be employed; (5) the dose of the drug administered can be readily controlled by varying concentration, current density, time and electrode area; (6) histamine administered iontophoretically forms depots in the skin; (7) it is adapted for home use for the technique can be easily carried out either by the patient without help or with the help of the family.

Previous investigations have shown that histamine introduced by iontophoresis into the skin forms depots in the pores of the skin. On the basis of the therapy of eleven patients with multiple sclerosis, one of whom had as many as fifty-five treatments on the anterior aspects of the forearm, 1 per cent histamine acid phosphate solution may be readily administered by electrophoresis with a current density of  $\frac{1}{2}$  milliamperere per square inch for fifteen minutes at a time. The following phenomena occur:

1. A typical histamine primary flush occurs within five to ten minutes after the drug is electrically administered.
2. Small doses decrease the diastolic pressure, while the larger optimal doses decrease both the systolic and the diastolic pressures.
3. In spite of the drop in blood pressure, the patients remain ambulatory.
4. The reaction of the patient is better to the higher doses and consists, in general, of increased muscular co-ordination and strength and improved use of the eyes, as far as vision is concerned.
5. An interesting phenomenon, apparently hitherto not observed, is the occurrence of secondary flushes. With the high doses employed, half of the patients reported frequent occurrence of a flush five to twenty-four hours after histamine iontophoresis. These secondary flushes provide further evidence that the electrical technique produces depots of histamine in the pores of the skin.

The iontophoretic technique is equivalent to intravenous drip therapy, with more flexibility. According to Brickner and Franklin<sup>9</sup> and Franklin and Brickner,<sup>10</sup> the basic notion in the therapy of multiple sclerosis "calls for continued vasodilatation of the vessels of the nervous system, as well as for the prevention of spasm. Both these measures should be enforced for twenty-four hours a day. A drug-free interval of even a few minutes would suffice for an attack."

It is believed that the technique now being developed may lead to the ultimate fulfillment of the criteria of therapy suggested by Brickner and Franklin.

The writer is indebted to Dr. M. B. Bender and Dr. Richard M. Brickner, who were kind enough to refer patients with multiple sclerosis for therapy.

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## DUST-SEAL

(Continued from Page 510)

There are no reliable statistics from which the incidence of nonreaginic dust sensitivity can be estimated. If it equals that of reaginic sensitivity in the atopic group (about 25 per cent), physicians may reasonably urge the use of only Dust-Sealed bedding and upholstery in all dwellings and hospitals. The simple Dust-Sealing of floor coverings is no problem.

### SUMMARY

A new product, Dust-Seal, has been found to immobilize allergenic house dust in floor coverings and other fabrics, as indicated by lowering of blood pressure, slowing of pulse rate and disappearance of allergic symptoms, in dust-sensitive persons.

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## SENSITIVITY TO MERCURIAL DIURETICS

### Report of a Case of Urticaria Due to Mercupurin

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IT is probably safe to say that mercury has been employed medicinally in a greater variety of compounds and by way of more routes of administration than nearly any other element. Mercury in various forms may be applied directly to the skin as a liquid or ointment, or by inunction or tattooing; it is also administered by mouth, by intramuscular and intravenous injection, and by rectal suppository. Interesting cases of sensitivity to mercury by injection were reported as early as 1895 by Jadasohn,<sup>31</sup> and constitute some of the early clinical material on which the concept of patch testing was based. Mercurial compounds are notorious epidermal sensitizers, and in several recent series of cases led all other cutaneous drugs as a cause of therapeutic dermatitis (Gaul,<sup>25</sup> Lane,<sup>33</sup> Underwood et al<sup>56</sup>). Moreover, sensitivity to mercury may be of extreme intensity. Not infrequently, cutaneous hypersensitiveness may be so great that patch tests with a 1:1,000,000 dilution of either organic or inorganic mercurial compounds may produce bullous reactions and even focal flares of distant dermatitis in some cases (Gaul<sup>25</sup>). Another example of the incredibly small quantities capable of producing severe manifestations is a case cited by Sulzberger.<sup>48</sup> One day after merely spending an hour in a room in which a small quantity of Mercurochrome had been spilled several hours earlier, this patient had generalized dermatitis, lymphadenopathy, prostration and high fever. Even pure metallic mercury has been responsible for cutaneous eruptions (Traub and Holmes,<sup>52</sup> Billo,<sup>7</sup> Bass<sup>4</sup>). Evidence of mercurial poisoning may accompany the contact dermatitis, as in a case observed by Samitz<sup>45</sup> due to ammoniated mercury ointment. Most recent reports of sensitization implicate cutaneous antiseptics, such as Mercurochrome (Pasher and Silverberg<sup>43</sup>), Mercurophen (Gross<sup>27</sup>), Merthiolate (Ellis and Robinson,<sup>10</sup> Hollander,<sup>20</sup> Lipson<sup>35</sup>), Metaphen (Belote and Marshall<sup>5</sup>), and phenyl mercuric nitrate (Hydrophen) (Wilson<sup>60</sup>). However, the mercury content of cosmetics may be responsible (Cifrián,<sup>15</sup> Schwartz and Peck<sup>16</sup>) and, as already mentioned, so may the mercury in dermatologic preparations as well as industrial contactants. Epidermal contact need not invariably produce dermatitis. In a woman observed by the author,<sup>57</sup> urticarial wheals occurred on the patient's hands, forearms and groin each time she applied ammoniated mercury ointment to her child's impetigo. A patch test with this ointment produced not a vesicular dermatitic response, but a typical urticarial wheal within twelve hours. Both local and distant cutaneous manifestations and even systemic allergic reactions have been noted to follow

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inunction of mercurial ointment (Billo<sup>7</sup>) and tattooing with cinnabar (Novy,<sup>40</sup> Sulzberger et al.,<sup>40</sup> Swinny<sup>51</sup>). The mercury contained in mercury amalgam dental fillings has been found to cause urticaria (Bass,<sup>4</sup> Markow<sup>56</sup>) and dermatitis, sometimes with stomatitis, from contact with the mercury during the dental manipulation (Blumenthal and Jaffé,<sup>9</sup> Traub and Holmes<sup>52</sup>). Mercurial rectal suppositories are also capable of eliciting allergic reactions (Blackford,<sup>6</sup> Kline and Seymour,<sup>32</sup> Fox et al.<sup>54</sup>).

In view of the length of this incomplete list of proved sensitivity to mercury, it is surprising that allergic reactions to parenterally administered mercurial diuretics are, in the opinion of all observers, rare. Thousands of injections have been given by some investigators<sup>32,36,54</sup> without noteworthy untoward effects. Some individual patients have been known to tolerate hundreds of doses over periods of several years without incident. The allergic manifestations, when they do occur, are quite varied, as will be noted below, and may be mild, alarming or even fatal.

### POSSIBLE MECHANISMS OF REACTIONS

However, it must be emphasized that drugs as physiologically potent as mercurial diuretics are capable of producing untoward reactions by a number of mechanisms. For clarity of analysis, it is profitable to consider these briefly. DeGraff and Nadler,<sup>16</sup> in a thorough review of the toxic manifestations of mercurial diuretics, classify them as fundamentally resulting from the associated diuresis or directly due to the drug. Such symptoms as disturbances of salt balance (particularly chloride depletion), precipitation of gout, and overdigitalization are considered the result of diuresis, while gastrointestinal complications (e.g., stomatitis, salivation, and hemorrhagic colitis), renal complications, anuria, chills, fever, and shock are traced to the drugs themselves. However, these authors point out that, in common with other potent drugs, individual susceptibility or idiosyncrasy occurs with mercurial diuretics, and that all commercially available drugs of this group have been implicated in isolated instances of alarming symptoms and even death, in some cases apparently due to susceptibility. Evans and Perry<sup>22</sup> classify the untoward effects under six headings: (1) local ulceration, due to seepage of the drug into perivenous tissues; (2) muscle pains, somnolence, delirium, occasionally coma, and sometimes tetany or epilepsy, due to chloride depletion resulting from the diuresis; (3) in digitalized patients, digitalis toxicity, due to mobilization of digitalis from edema fluid; (4) various reactions such as fever, rashes, tremor, tinglings in the arm, stomatitis, nausea, vomiting, diarrhea, colitis, sensations of thoracic constriction, swelling of the lips, and anuria, some of which are undoubtedly on the basis of a direct toxic effect; (5) precipitation of an attack of gout; and (6) death. They believe the cause of death to be obscure, but state that it may be an acquired sensitivity. However, none of their cases died after his



first injection of a mercurial diuretic, suggesting acquired sensitivity as a probable cause of the phenomenon. According to Marshall<sup>37</sup> mercurial diuretics may cause tetany, manifested by muscle "cramps" and carpopedal spasm, as a result of low blood calcium levels. Such electrolyte imbalance may occur prior to diuresis, although obviously it will be enhanced by excessive urine flow, and may explain one of the modes of exitus. The nature of the required therapy is apparent.

It should be noted that these drugs are capable of producing death in animals by reason of the primary poisoning effect of mercury on the heart, producing ventricular fibrillation. That this mechanism applies to some human fatalities was clearly shown by Volini et al.<sup>58</sup> On the basis of animal experiments, Chapman and Shaffer<sup>13</sup> found Mercuhydrin to be less toxic than Mercuphylline or Mersalyl and theophylline, and that its toxicity was still further reduced by ascorbic acid given simultaneously. They suggest that since nonfatal hypersensitivity reactions, such as tachycardia or premature ventricular systoles occurring after intravenous administration, may be premonitory signs of a fatal reaction, Mercuhydrin combined with ascorbic acid is the diuretic preferred in such cases. This suggestion requires confirmation. It is also possible that death may occur by respiratory failure secondary to the impaired cardiac action which is presumed to lead to anoxia through lowering of the blood pressure. It has been emphasized<sup>18</sup> that in the majority of deaths in man following the administration of mercurial diuretics, the blame could be placed on the moribund condition of the patient, on digitalis poisoning, on depletion of chloride, or an oliguria or anuria leading to faulty elimination of the diuretic itself, or on the presence of kidney impairment sufficient to prevent adequate excretion of the drug or to predispose to such damage by the mercurial. Certainly, sensitivity to mercurial compounds as a cause of death must be comparatively rare, and apparently occurs with no greater frequency than with other drugs in susceptible patients. On the other hand, cutaneous eruptions produced by mercurial diuretics are now probably on an allergic basis, the true mercurial dermatitis being said no longer to occur with the more rapidly excreted mercurials now in use.

The possibility of the nonspecific syndrome of "speed shock" (Hyman<sup>30</sup>) has been considered by a number of authors, but ruled out by most on the basis of the small quantities involved and the time taken for the injection. In reply to this, Hyman points out that the maximum permissible rate of injection will vary depending on the nature of the substance being injected and on the condition of the patient, among other factors. In any case, demonstration of the incoagulability of the blood postmortem would constitute evidence favoring a diagnosis of "speed shock." This was not done in any of the cases mentioned below. Wexler and Ellis<sup>59</sup> maintain that fatal and immediate nonfatal reactions are probably due to the direct toxic effect of mercury on the heart, while delayed nonfatal reac-

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tions are incident to the physiologic effects consequent on the diuretic action. Large (and unphysiologic) doses are not always necessary to produce mercurial toxicity: Derow<sup>17</sup> observed a patient in whom the third injection of 2.9 c.c. Salyrgan, making a total of 5.7 c.c., was followed by clinical acute mercury poisoning. The fact that mercury produces pronounced vasodilatation as a result of paralysis of the sympathetic nerves was suggested by Lesser<sup>34</sup> as early as 1888, and was supported, as regards the skin, by the histologic studies of Almkvist.<sup>1</sup>

Lacking, or having no opportunity to obtain, direct confirmation of hypersensitiveness, some authors employ the phrases, "One can only speculate that the reaction is probably an anaphylactic one" (Tyson<sup>55</sup>), or the clinical picture "suggests that the cause of death was an anaphylactoid phenomenon" (Wolf<sup>61</sup>), or the individual "apparently possessed an increased susceptibility to the drug" (Rosenthal<sup>44</sup>), or, "We must assume that this patient possessed a marked degree of susceptibility to the drug" (Andrews<sup>2</sup>). The nature of the evidence favoring an allergic pathogenesis of some reactions, and the possible mechanism of its origin will be considered in the Discussion.

A complete review of all the untoward reactions to mercurial diuretics would be out of place here. Hence only those reports in which an allergic basis was demonstrated, suspected or considered, are included.

### FATALITIES

In 1931, Wolf and Bongiorno<sup>61</sup> reported the sudden death of a four-year-old child immediately after his sixth intravenous injection of Salyrgan. Since the previous injection, one week earlier, had been followed by chills, fever and a morbilliform rash, an anaphylactoid phenomenon was thought to be the cause of death. In reporting the autopsy findings of a case dying after the second dose of Salyrgan, Rosenthal<sup>44</sup> suggested that the patient apparently possessed an "increased susceptibility" to the drug, since only a small quantity had been given. Molnár<sup>39</sup> came to the same conclusion in his patient who died twenty minutes after an intraperitoneal injection of 2 c.c. of Novurit (Mercupurin), since the autopsy findings failed to explain the sudden death. Cadbury<sup>12</sup> reported two fatalities and two severe nonfatal reactions from Salyrgan. Two children with nephrosis were observed by Greenwald and Jacobson,<sup>26</sup> each dying one to five minutes after the third injection of Neptal (Salyrgan). Necropsy in one case revealed generalized lymphoid hyperplasia and other findings consistent with an anaphylactoid death. Tyson's<sup>55</sup> case died one minute after the second intravenous injection of Mercupurin in two days, and one of Kline and Seymour's<sup>32</sup> died in convulsions after the second dose of Salyrgan, although one and one-half months had elapsed after the first injection. In the four fatalities reported by Brown et al<sup>10</sup> death occurred within one to four minutes of an intravenous injection of Mercupurin, and was therefore independ-

ent of such factors as massive diuresis, chloride loss or disturbance of electrolyte balance; in three patients, immediate reactions to intravenous injections had been noted prior to the final one. Barker and his co-workers<sup>3</sup> also observed four immediate deaths after intravenous mercurials, including one after an initial dose of Mercupurin, and one after the first dose of Salyrgan (although Mercupurin four months earlier had caused unconsciousness and asystole, followed by short runs of auricular fibrillation). Necropsy findings in each case failed to explain the sudden death.

In a review article in 1942, DeGraff and Nadler<sup>16</sup> accumulated a total of twenty-six deaths attributed to mercurial diuretics reported in the literature over a period of sixteen years. Omitting those patients seriously ill before the injection, Evans and Perry<sup>22</sup> found fifteen instances of sudden deaths in the literature since 1931, and added six cases, four of which had nephrotic syndromes, observed between 1936 and 1943 in the hospitals in one section of London. Although they held the cause of death to be obscure, they stated that it may be an acquired sensitivity. Wexler and Ellis<sup>59</sup> reported two instances of death, each within a few minutes after an intravenous injection of Mercupurin, although the patients had tolerated 164 and thirteen previous injections, respectively. Necropsy revealed no immediate cause of death in either case. Ben-Asher<sup>6</sup> attributed his fatality to extreme hemoconcentration, contributed to by a high environmental temperature, rather than to an allergic mechanism.

#### CUTANEOUS MANIFESTATIONS

Those cases in which the mercurial sensitivity was manifested as a cutaneous eruption appear, in general, to have been more carefully considered from the allergic standpoint.

The first report of urticaria from mercurial diuretics appears to be that of Turnai,<sup>54</sup> following an earlier reference to the same case by Engel and Epstein.<sup>21</sup> After a number of injections of Salyrgan and Novurit (one of which caused transitory paroxysms), a patient with luetic aortic insufficiency had a pruritic bluish-red papular eruption over the neck and trunk within twenty seconds of a Novurit injection. This was followed by a hemorrhagic urticaria, persisting for five or six weeks, and healing with pigmentation. Salyrgan was tolerated for three months without incident, but a trial of Novurit was again followed by urticaria chronica perstans, as well as by a deleterious effect on the general condition resulting in the death of the patient. Turnai attributed the cutaneous outbreak to an allergic sensitization to Novurit. Urticarial reactions have been also described by Blackford<sup>8</sup> and Kline and Seymour.<sup>32</sup> The former's case, under treatment for congestive heart failure, responded with nausea, headache, vertigo, visual disturbances, pruritus, wheals on the forearms, dyspnea, cyanosis, and vomiting to an injection of 2 c.c.

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of Mercupurin and 10 c.c. of aminophylline. A repetition of the injection without the aminophylline was followed by even worse effects. Salyrgan by vein was better tolerated, but still caused symptoms, while a Salyrgan-theophylline rectal suppository produced severe urticaria. Oral tablets of the latter drug were repeatedly tolerated. One of Kline and Seymour's<sup>32</sup> cases had transient urticaria after eight consecutive intravenous injections of Mercupurin, and a diffuse erythematous rash after two subsequent ones, although twenty-two preceding injections of Salyrgan and Mercupurin had caused no untoward effect.

Another of their cases had transient erythema progressing to exfoliative dermatitis with repeated Salyrgan dosage, while a third had a generalized morbilliform rash accompanied by chills, fever, dyspnea, cyanosis, nausea and vomiting after intravenous Mercupurin as well as after Mercurin rectal suppositories. Two additional cases demonstrated no skin manifestations, but were characterized by chills, and by death in convulsions, respectively. While no testing was performed, the fact that one or more intravenous injections had been administered in each case without mishap led the authors to assume that sensitization might be the cause. Although Fox, Gold and Leon's<sup>24</sup> case was known to have urticaria due to hypersensitiveness to a wide variety of foods, her reactions to intravenous Mercupurin and to Mercurin rectal suppositories were not urticarial, but erythematous, at times blotchy in distribution and at other times diffuse. Along with this there were fever, conjunctival congestion, paresthesias, pruritus, numbness of the cheeks and tongue, sensations of substernal constriction and epigastric pressure, salivation, vomiting, swelling of the lips and blurring of vision. Scratch tests with full-strength Mercupurin and Salyrgan were negative. Clinical reactions to Salyrgan or Neptal were very mild, and 196 weekly doses of Salyrgan each containing approximately 80 mg. of mercury, were tolerated. Observation of their case over a period of time revealed the following: as little as 0.1 c.c. of Mercupurin (containing 4 mg. of mercury) produced severe reactions with most of the symptoms mentioned, as did Mercurin rectal suppositories; the reactions were unrelated to massive diuresis, to theophylline and to ionized mercury, such as contained in mercuric chloride or mercuric oxycyanide, and their duration and severity depended on the dose and type of mercurial; and the hypersensitiveness did not seem to change over a period of years. In addition to the sensitivity, symptoms characteristic of mercury poisoning could be produced with larger doses of any mercurial.

Nine cases of erythematous eruptions, all with itching, one being morbilliform in character, were reported by Burrows and Stokes<sup>11</sup> after repeated injections of Neptal (closely related to Salyrgan). In each case, a patch test was positive at the time of, or shortly after, the reaction. Later, in every case, after a brief rest period, the patch test was negative, and at this time intravenous administration of the drug gave no untoward

effects. In one of the earlier reports, Snell and Rowntree<sup>47</sup> described four cases of widespread purpura following injections of Merbaphen. Although these authors dismissed the possibility of an allergic mechanism and attributed the phenomena to the effects of the drug on the capillaries, a number of instances of purpura have been shown to be due to drug allergy (Urbach and Gottlieb<sup>57</sup>). Engel and Marcusson<sup>20</sup> reported two cases with hemorrhagic eruptions and diffuse dermatitis following injections of Salyrgan. Zeiler<sup>62</sup> found the incidence of morbilliform and scarlatiniform rashes to be 0.6 per cent in a series of several thousand injections of Merbaphen to syphilitic patients. Since other mercurials subsequently caused no symptoms, he implicated the complex Merbaphen molecule rather than the mercury itself.

#### OTHER MANIFESTATIONS

Asthmatic manifestations from mercurials have apparently been reported only twice. Parent<sup>42</sup> observed cough, asthmatic respiration, cyanosis, convulsions, and incontinence after the first dose of Esidrone. The patient recovered and tolerated Mercupurin thereafter, as he had previously. Wexler and Ellis<sup>59</sup> described typical asthmatic attacks with the classical physical findings, occurring one to two hours after Mercupurin administration in two cases. They attribute these reactions indirectly to the diuretic action of the drug, incident to the transitory increase in plasma volume, producing pulmonary edema or bronchial congestion, and resulting in an asthmatic type of respiration in patients with little cardiac reserve. They hold that the mechanism in these two instances was one of a cardiovascular disturbance essentially the same as in the patients who develop pulmonary edema, in which condition, of course, asthmatic breathing may dominate the clinical picture. These authors also reported seven additional cases of alarming nonfatal reactions, chiefly with cardiorespiratory manifestations, including two episodes of pulmonary edema.

Other severe reactions have been blamed on hypersensitiveness. Tyson's<sup>55</sup> case may be considered a "near fatality" with convulsions and coma one minute after an injection of 1 c.c. of Esidrone, although several preceding doses were without these effects. Respiration apparently ceased, and the heart sounds could not be heard. The patient recovered, but only after a period of coma, mania and projectile vomiting lasting for hours. The case observed by Andrews<sup>2</sup> had headache before the completion of the first injection of 0.5 c.c. of Salyrgan, followed in fifteen minutes by loss of consciousness, clonic spasms, marked vasomotor phenomena, and vomiting. In the ensuing twelve hours, five similar episodes occurred. Of ninety-two patients receiving 1,729 injections of Mercuhydrin and Mercupurin, Modell et al<sup>38</sup> noted only two with systemic reactions. In one, faintness and giddiness occurred for thirty minutes after Mercupurin intravenously but not intramuscularly; Mercuhydrin was tolerated. In

the other, chills and fever appeared two hours after Mercuhydrin by either route of administration, but not after Mercupurin.

The following case is thought worthy of description because it is the fourth in the literature in which urticaria was due to a mercurial diuretic and the second in which urticaria was the dominant clinical manifestation; because the hypersensitiveness was proved by skin testing, this being the first such case to be subjected to this proof; because of the successful application of the patch-abrasion or scratch-patch test; and because the test itself was capable of producing a focal reaction in the form of further urticaria.

#### CASE REPORT

J. A. D., a nineteen-year-old white man, was admitted to the hospital with a diagnosis of nephrotic stage of chronic glomerulonephritis. The past, personal, and family histories were negative for all types of allergic diseases. Physical examination and laboratory study confirmed the diagnosis, with, among other findings, marked dependent edema, ascites, intense albuminuria, and hypoproteinemia. Several intravenous infusions of human serum albumen were tried. When significant clinical improvement did not occur, ammonium chloride was given by mouth, and four injections of Mercupurin\* were administered, the first intramuscularly and the subsequent ones intravenously. Adequate diuresis followed each, but the edema never entirely subsided, and fluid reaccumulated each time within a few days. No untoward effects were noted except possibly mild transient headaches, although the patient complained of these at other times as well. The fifth injection of Mercupurin (the fourth intravenous) was given about one week after the preceding one. Approximately seven hours later, the patient was awakened from sleep by generalized itching, most intense in the calves of the legs. Shortly thereafter, a rash appeared in the region of the left shoulder and left thorax, and in the course of the next few hours spread to involve the face and most of the trunk and all extremities. Its appearance was typically urticarial, with raised, pink wheals of roughly rounded outline, except where confluence of the lesions produced gyrate patterns. New wheals appeared and old ones faded at intervals. White blood cell count at this time was 6,600 per cu. mm., with 3 per cent eosinophiles. The temperature rose to maximum of 101.6° F., coinciding with the peak of the rash, and remained between 99° and 100° F. for three days, although it had consistently been normal before. The rash was treated by means of calamine lotion locally, and mild sedation administered. The urticaria faded within about twenty hours, leaving a patchy erythema which persisted for two days. Aside from the intense itching and mild weakness, the patient had no subjective complaints.

Seventeen days later, because of increasing edema, an intravenous injection of 2 c.c. of Mercupurin was again given. Within a few minutes, generalized itching appeared, followed by erythema and general urticaria, along with firm deep swellings of the chin, cheeks, shoulders, and forearms. Epinephrine was administered subcutaneously in divided dosage, but new urticarial wheals continued to appear at irregular intervals, particularly over the upper half of the body, for three days, and during this period the skin was not completely free of urticaria at any time. The temperature was again elevated.

After the subsidence of this episode, skin testing was performed. Patch tests with full strength Mercupurin and Salyrgan-theophylline were negative after forty-eight hours of contact, and when observed after another forty-eight hours. Scratch tests were unsatisfactory, since at the end of twenty minutes the edges of the

\*Now known as Mercuzanthin.

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scratch seemed acutely inflamed, with intense erythema for a short distance, in both the patient and three control subjects. Mercurial compounds are not suitable for intradermal testing due to their primary irritant nature.

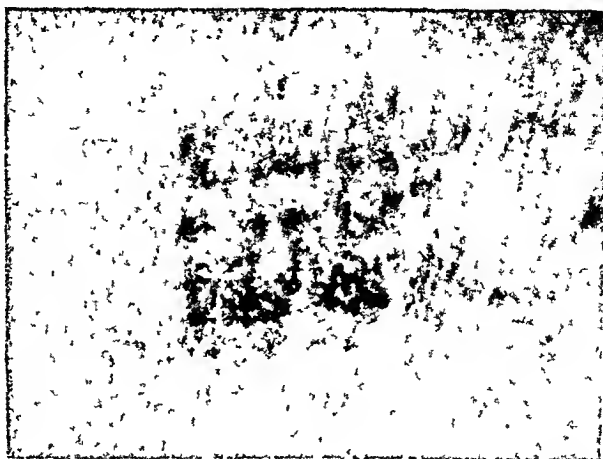


Fig. 1. Reaction of patient to patch-abrasion (scratch-patch) test with undiluted Mercupurin sixteen hours after twenty hours of contact.

TABLE I. REACTION OF PATIENT AND CONTROL SUBJECTS TO MERCURIAL DIURETICS AND AMMONIATED MERCURY OINTMENT

	Mercupurin		Salyrgan-Theophylline		Ammoniated Mercury Ointment, U.S.P.
	Patch Test	Scratch-Patch Test	Patch Test	Scratch-Patch Test	Patch Test
Patient, J. A. D.	neg.	str. pos.	neg.	wk. pos.	neg.
P. E. K. (allergic)	neg.	neg.	neg.	neg.	neg.
S. G.	neg.	neg.	neg.	neg.	neg.
A. B.	neg.	neg.	neg.	neg.	neg.
B. H. D.	neg.	neg.	neg.	pos.	neg.

Hence a patch-abrasion or scratch-patch test (Tucker and Thomas<sup>53</sup>) was performed. For this purpose, after cleansing of the skin, three or four superficial scratches were made in a crosshatch pattern on the skin of the forearm, insufficient to draw blood. Over this was placed a square of white blotting paper approximately 1 cm. square, saturated with undiluted Mercupurin solution. About two hours later, the patient complained of generalized itching, and soon thereafter noted urticarial wheals over the arms (including the region adjacent to the test), anterior chest, upper back, and face. This outbreak was similar to his previous episodes except that it was not generalized and that the individual wheals were possibly somewhat smaller. These symptoms were not made known until the test was read, when the hives were beginning to fade. The patch was removed at the end of twenty hours, at which time the entire test area was the site of sharply demarcated swelling of a firm consistency, along with moderate erythema. Observed daily, these changes persisted with gradually increasing intensity for another forty-eight hours, then declined gradually. A photograph of the reaction was taken thirty-six hours after the application of the drug, or sixteen hours after the removal of the patch (see Fig. 1). The patient was tested similarly with injectable Salyrgan-theophylline and had a similar reaction although less intense, persisting for three days.

In order to confirm the specificity of the reaction, four control subjects, one

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with allergic bronchial asthma and three with various diseases, were tested by the same techniques. The results are shown in Table I. The negative scratch-patch tests revealed only barely discernible lacerations at the sites of the tests at the time of the removal of the patches, and even this was gone in a day or two. The reaction of patient B.H.D. to Salyrgan may be commented upon. This man, with hypertensive heart disease in congestive failure, had had three injections of Salyrgan-theophylline previously, and had a number subsequently, all without untoward incident. The significance of the positive skin test in this case is not known.

### DISCUSSION

There can be no doubt, in view of the time relationships involved, that the urticarial eruptions in this case were due to the injected Mercupurin. The patient had never previously suffered from urticaria. He was also fed, in as nearly the same quantity and same method of preparation as possible, those foods which he had taken before the appearance of the rash. No reaction occurred. An allergic mechanism is proved by the positive response to the patch-abrasion test, and even more decisively by the focal or urticarial reaction to this test. While the actual patch used in the test was discarded, comparable ones prepared from the same material were found to hold, at most, less than 0.1 c.c. of Mercupurin solution (containing 4 mg. of mercury). While it is not possible to determine how much of this was absorbed, the quantity must have been quite small, and yet it was capable of causing a fairly extensive urticaria. It is inconceivable that such an amount could produce its effects either by direct toxic action of the mercury or by its effects on blood volume, diuresis (which did not ensue), electrolyte or water balance.

The negativity of the patch test is not surprising, since epidermal sensitivity is not anticipated. Scratch testing was unsatisfactory. However, the scratch-patch test proved to be of value in confirming the allergic nature of the case. This method of testing was successfully employed recently with such drugs as sulfanilamide (Fisher<sup>23</sup>) and penicillin (Urbach and Gottlieb,<sup>57</sup> O'Donovan and Klorfajn<sup>41</sup>). This technique should probably be employed more extensively in instances of suspected drug allergy, in order to define more precisely its limitations and the control of the variables involved.

It is beyond the scope of this paper to discuss the advisability of employing mercurial diuretics in the presence of demonstrable renal disease. Opinions apparently differ on this point. However, a considerable proportion of the reported untoward reactions occurred in patients with nephrosis or nephritis, although it is likely that these drugs are used far more frequently in cases of cardiovascular disease. Tyson,<sup>55</sup> Evans and Perry,<sup>22</sup> and others suspect that this may be connected in some way with the altered blood proteins present in the former patients, with decreased total blood protein values, an actual or relative reversal of the albumin-globulin ratio, and perhaps even a change in the quality of the protein. While no fatalities have been reported after the intramuscular injection of a mercurial diuretic, and while some authors have recommended that



injections of mercurial diuretics, in cases of nephritis and possibly other diseases associated with low plasma protein levels, be restricted to the intramuscular route in order to prevent severe reactions, experience with this avenue of administration has not been sufficient to know whether this precaution will be effective. It has even been recommended that the susceptibility of the patient be tried first by means of two or three intramuscular doses in increasing quantity before trying intravenous injections.

However, Greenwald and Jacobson<sup>26</sup> suggested that the first intramuscular injections may actually be responsible for sensitization, while a change to the intravenous route may cause shock in human beings. Chastain and Mackie<sup>11</sup> were unable to confirm this hypothesis in experiments on dogs, but the well-recognized difficulties of allergizing animals to drugs vitiates the applicability of this work as regards clinical experience.

It is apparent that only a very small percentage of serious untoward reactions have occurred after the first injection of a mercurial (Andrews,<sup>2</sup> Cadbury,<sup>12</sup> Barker et al.,<sup>3</sup> Sundaram<sup>50</sup>), the vast majority appearing after the third or subsequent administration. This, of course, constitutes a point of indirect evidence favoring a mechanism of allergization as the cause. Equally important, however, is the conclusion that physicians should be forewarned not to neglect the possibility of an untoward reaction merely because previous injections were tolerated without incident. Also, in a number of reported cases, minor reactions, chiefly cutaneous in nature, but also chills and fever and transitory cardiac arrhythmias, preceded the ultimate, serious or fatal reactions. Such danger signals should constitute a warning of possible sensitization, a basis for careful review of the therapy of the individual case and, in all probability, a strong indication for the discontinuance of mercurial drugs.

A review of the reported instances of suspected sensitivity to mercurial diuretics reveals the extreme paucity of skin tests. Of course, the cases ending fatally gave no opportunity, although some of them had immediate nonfatal reactions preceding the fatal one. Had these been tested at this time, it is possible that valuable information might have been gained. It is thought that cutaneous eruptions produced by mercurial diuretics in recent years are probably allergic in character rather than on the basis of a true mercurial dermatitis, which is said not to occur since the employment of the more rapidly excreted theophylline-containing mercurials. The positive patch tests uniformly obtained by Burrows and Stokes<sup>11</sup> are of particular interest, but it must be recalled that they dealt exclusively with instances of erythematous skin eruptions. The reversal of the patch tests after a short rest period (without hyposensitization) and the concomitant tolerance of the drug is rather unlike the usual experience with drug allergy, and in direct contrast to the findings of Fox, Gold and Leon,<sup>24</sup> whose patient's hypersensitiveness did not seem to change over a period of years. Their clinical observations led Burrows

and Stokes<sup>11</sup> to conclude that a failure of diuretic response to continued frequent injections of mercurials appeared to enhance accumulation of the metal and subsequent cutaneous sensitization. Such cumulative effects seemed to depend on too high or too frequent dosage, renal impairment, congestive changes, prolonged administration, and especially deficient elimination of the drug (i.e., poor diuresis). Obviously, this explanation does not apply to the majority of cases. Nevertheless, they believe patch testing to be useful when accumulation of the drug is suspected or when continuation of the therapy is desirable after cutaneous sensitization to mercury, and that the latter need not contraindicate the subsequent employment of these diuretics in adjusted dosage after a short interval. With this conclusion most authorities disagree,<sup>15</sup> and certainly in the case reported herein, a rest period of seventeen days not only failed to prevent symptoms, but was actually followed by a more severe and more promptly appearing reaction. The marked shortening of the latent period between the administration of the drug and the appearance of urticaria on the two occasions is worthy of note. It seems safe to conclude that the occurrence of even mild reactions in the course of treatment should be considered a contraindication to further exhibition of these drugs. Such a precaution would have prevented a number of the reported fatalities.

Hyposensitization to mercurial diuretics has not been reported. None of the reported cases, except the present one, appears to have been treated by antiallergic measures.

Two other suggestions have been advanced to prevent untoward incidents, viz., a change in the mercurial diuretic employed, and a change in the route of administration. Without going into detail on these points, it may be stated that while some patients sensitive to one mercurial may tolerate another with impunity (e.g., Fox et al,<sup>24</sup> Modell et al,<sup>38</sup> Turnai,<sup>54</sup> Parent<sup>42</sup>), in many cases this will not be true (Blackford,<sup>8</sup> Barker,<sup>3</sup> Wexler and Ellis<sup>50</sup>). In the former type, the hypersensitiveness would appear to be related to the organic structure of the drug; in the latter, to the mercury itself. In the case reported here, it should be noted that a scratch-patch test with Salyrgan-theophylline was positive, although the drug itself was not administered. According to Wexler and Ellis,<sup>50</sup> there is no indication that changing from one preparation to another is a safeguard against fatal reactions. Likewise, changing the route of administration to the intramuscular or rectal, while sometimes effective, will by no means always prevent reactions (Blackford,<sup>8</sup> Kline and Seymour,<sup>32</sup> DeGraff and Nadler,<sup>16</sup> Barker et al,<sup>3</sup> Brown et al,<sup>10</sup> Fox et al,<sup>24</sup> Modell et al<sup>38</sup>). This statement seems to be particularly true of those patients who have shown definite allergic reactions, such as urticaria, rash and fever. There is no reason to think that diluting the drug with physiologic solution of sodium chloride prior to injection, as has sometimes been done, will in any way reduce the incidence of untoward episodes.

It seems likely that reactions occurring promptly after administration of the drug are based on one of three possible mechanisms: allergy, toxicity, and "speed shock." In many instances (Wolf and Bongiorno,<sup>61</sup> Greenwald and Jacobson,<sup>26</sup> Tyson,<sup>55</sup> Barker<sup>3</sup> and Brown,<sup>10</sup> among others), the untoward reactions and even fatalities occurred within one or two minutes after the injections. In such cases, attempts to attribute the untoward action to the physiologic effects of the drug incident to the diuresis, with the ensuing alterations in plasma volume, electrolyte and water balance, would seem to be disproved by the very rapidity of the reaction. Wexler and Ellis<sup>59</sup> hold that the asthmatic manifestations which they observed in two cases were accounted for by pulmonary edema or bronchial congestion in patients with a low cardiac reserve. However, while no final statement can be made, the facts that the attacks appeared in one or two hours, that they occurred only after the last of several injections, that relief was afforded in one case by epinephrine and that asthma is so frequently a symptom of hypersensitiveness, make an allergic basis for these findings at least equally plausible. Unfortunately, no testing was done. Primary toxic action of the mercury may be ruled out in many cases by a consideration of the total dosage received and by the clinical (or necropsy) findings. "Speed shock" would appear to depend largely on the rate (and quantity) of intravenous injection, but could be confirmed, even after death, by following a suggestion by Hyman.<sup>30</sup> Since the freshly drawn blood is rendered incoagulable by "speed shock," it would be well to make this simple observation in cases of these unfortunate therapeutic accidents.

Thus, there remains the allergic explanation. The fact that most reactions and most fatalities occurred after a series of injections with mercurial diuretics would lend support to this concept. Other evidence favoring this mechanism has been discussed above.

Finally, the possibility that mercury in these diuretics may act as a hapten remains to be considered. Haxthausen<sup>28</sup> showed that mercury, as well as other simple chemical compounds, is sometimes capable of producing cutaneous hypersensitiveness of eczematoid character in human beings in certain concentrations only after conjugation with foreign protein—among other substances, animal serum. It has already been noted that many of the untoward reactions, including that here described, occurred in patients with lowered plasma protein levels and abnormal albumin-globulin ratios resulting from the underlying disease. Greenwald and Jacobson,<sup>26</sup> Tyson,<sup>55</sup> and Evans and Perry<sup>22</sup> favor the concept that the mercury functions as a hapten, conjugation possibly taking place more readily with a lowered or altered plasma protein.

#### SUMMARY AND CONCLUSIONS

Mercurial diuretics may act as allergens, giving rise to a considerable variety of clinical manifestations and even fatalities. However, these

potent drugs may also produce untoward reactions by any one of several other mechanisms, of which may be mentioned primary toxicity of the mercury, especially on the heart, disturbances of plasma volume and fluid balance, electrolyte imbalance, "speed shock," overdigitalization and renal complications. Hence, it is incumbent upon the physician to study each such case as carefully as possible in an effort to determine the causé. From the allergic standpoint, patch-abrasion and patch tests would appear to be the most informative.

Fortunately, the over-all incidence of untoward reactions to these valuable drugs appears to be low. A reliable method of predicting untoward or fatal reactions in human beings is not available.

A case is reported in which generalized urticaria followed the fifth and sixth injections of Mercupurin, being the second case in the literature in which urticaria was the dominant clinical manifestation of hypersensitiveness to a mercurial diuretic.

The etiology of the eruption was confirmed by a positive patch-abrasion (scratch-patch test). The minute amount of the drug absorbed from the test site evoked a focal reaction in the form of further urticaria. The value of this method of testing is emphasized. It is recommended that the scratch-patch test be more extensively employed in suspected drug allergy.

Hypersensitiveness to mercurial diuretics is most likely to be manifest by cutaneous eruptions, but there is reason to suspect that chills and fever, asthmatic syndromes, convulsions, and death may occur on an allergic basis. The more serious reactions are not infrequently preceded by minor episodes, chiefly cutaneous, and these should constitute a contraindication to further mercurial therapy.

Allergic reactions are more likely to occur on multiple injection (usually after more than two), in patients with the nephrotic syndrome, with lowered plasma protein values and abnormal albumin-globulin ratios. A hapten mechanism is plausible.

Once an untoward, and particularly an allergic, reaction to a mercurial diuretic has occurred, the following, although sometimes effective, cannot be depended upon to prevent further episodes: a change in the drug employed, a change in the route of administration, or allowing a "rest" period. Dilution of the drug with physiologic saline solution has proved ineffectual for avoiding such effects.

The clinical features, recognition, and mechanism of hypersensitiveness to mercurial diuretics are discussed.

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SEPTEMBER-OCTOBER, 1948

## A COMPARATIVE STUDY OF COMMERCIAL NEBULIZERS

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NUMEROUS asthmatic patients during the past decade have stated, in giving their history, that they have tried inhalation of nebulized ephinephrine solution without relief, even in attacks of mild to moderate severity. Investigation invariably revealed that they had used a defective nebulizer or one of inadequate design. Some had tried several types and usually attributed success or failure with a certain model to the solution used rather than to the instrument. Matzger,<sup>14</sup> in 1935, stated that "a considerable quantity of vapor without droplets must be produced," and Graeser,<sup>13</sup> in 1939, reported "failure of the procedure in many instances is due to an inefficient atomizer."

Very little information is to be found regarding the characteristics of the various nebulizers commercially available. The Council on Physical Medicine has examined and accepted only three, the DeVilbiss Nos. 40 and 44<sup>10</sup> and the Holmspray No. 630.<sup>11</sup> Richards, Barach and Cromwell<sup>16</sup> found both the Vapco and the Vaponefrin models satisfactory, stating that the Vaponefrin produced a somewhat more voluminous stream. Stacey<sup>17</sup> used the DeVilbiss No. 40 and the Parke-Davis Adrenalin Vaporizer for nebulization of sulfonamide solutions but made no comment as to their efficiency. Abramson<sup>2,3</sup> has mentioned the DeVilbiss No. 40, the Vaponefrin, the Asthmamist, and the Ailene as being satisfactory, and states that the unpublished data of Bryson indicates that the particle size distribution of the first three is approximately the same. He stated that the particle radii in these models vary from 0.3 to 2 microns, not counting a certain amount of "rain" due to imperfect construction. In another paper<sup>4</sup> Abramson states that 50 per cent glycerol formed stable mists with the DeVilbiss No. 40, the Vaponefrin, and the Parke-Davis table model. The mist from the DeVilbiss No. 40 contained particles with diameters as follows: below 2 microns, 7.2 per cent; 2 to 6 microns, 65.5 per cent; 6 to 8 microns, 18 per cent; 8 to 38 microns, 9.4 per cent. These figures are at variance with those of Bryson, probably because, as Abramson states, this method yields a preponderance of larger droplets. Presumably the percentages refer to numbers rather than total mass of droplets in each group. Bryson, Sansome, and Laskin<sup>6</sup> give the average particle radius of the DeVilbiss No. 40 as 0.54 microns, with a range of 0.24 to 1.18. Barach et al<sup>5</sup> state that the Vaponefrin model delivers a majority of particles under 1 micron—whether diameter or radius is not stated. Only a negligible amount of medicament is returned in the expired air. Castex et al<sup>8</sup> used a nebulizer of their own design which was presumably satisfactory. Mutch<sup>15</sup> found the Collinson nebulizer satisfactory.

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## COMMERCIAL NEBULIZERS—HARSH

It was felt that it would be of service to acquaint the medical profession with certain details of the performance of the various models of nebulizers on the market. Since nebulizers are at present being put to a variety of uses, no one type is likely to be best for all purposes, although, as will be seen, some are capable of modification to increase their versatility.

Complete or partial failure of a given model could be due to (1) the production of an insufficient amount of mist, (2) too many large particles which do not get beyond the mouth and pharynx, and/or (3) a preponderance of actual vapor or of particles so small that they are exhaled. This latter effect may be due, in part, not to the nebulizer itself, but to the use of a solution which contains an insufficient amount of substances which lower the vapor pressure and thus enhance the permanence of the mist. The reduction in size of aqueous particles after they are generated is influenced by the temperature and relative humidity of the surrounding air. Mutch<sup>15</sup> states that the life of an aqueous particle of 2 microns diameter in dry air is only 0.0006 seconds. It obviously takes far longer than that for a particle to travel from the tip of the jet to a point in the respiratory tract where the relative humidity is 100 per cent. Even a glycerin particle does not last long in dry air although it may actually grow in moist air. It should be noted also that particles which lodge in the alveolar ducts and sacs have no local effect in relieving bronchospasm and are effective only as they are absorbed into the blood stream. According to Findeisen,<sup>12</sup> 84 per cent of particles of 2 microns in diameter, are deposited in these locations.

### PROCEDURE •

Nebulizers containing small amounts of distilled water were weighed before and after 500 compressions of the hand bulb, and the weight delivered by one squeeze of the bulb was calculated. The averages for the samples of each brand tested are shown in Table I. The variation among models of the same brand will be discussed later. The results are naturally influenced by the volume of the hand bulb. The capacity of the bulb supplied with each model is shown in the table. For the nebulization of solutions by pressure from an oxygen tank or by compressed air, the time required to nebulize 1 c.c. of water is more pertinent. The values obtained by oxygen pressure with the flowmeter set at 8 liters per minute are shown in the table. Also shown are values obtained with a small air compressor, manufactured for the purpose by the Selrodo Company and said by the company to generate 40 pounds pressure per square inch.

A few samples tested delivered visible droplets. This is recorded in the table. If the amount was not sufficient to be considered important, a 1-plus is recorded. Amounts of more serious proportions are appropriately indicated.

Accurate measurement of particle sizes in a mist is a difficult technical procedure. Furthermore, the size of the particles generated will vary with



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TABLE I. COMPARISON OF COMMERCIAL NEBULIZERS

No.	Model	Number Tested	Mg. in One Puff	Capacity of Bulb c.c.	Seconds to Nebulize 1 c.c. H <sub>2</sub> O		Radius of Particles (Microns)**		Drop-lets
					O <sub>2</sub> at 8 l/min.	Comp. Air	Median	Largest	
1	Breathesay	2	13.0	76	35	31	15	175	0
	Breathesay No. 2		7.9	49	31	30	19	250	0
	No. 1 with L-tube	1	7.2		72	68	13	78	0
	No. 1 with carburetor closed	1	3.0		182	155			0
2	Asthma Nefrin	3	2.84	65	101	98	8	212	++(1)
	best with L-tube		3.0		100	137	10	80	+(1)
3	Vaponefrin	6	2.1	65	104	169	16	127	0
4	Pen-i-sol	2	1.7			350			0
5	DeVilbiss 40	6	1.6	61	225	187	13	132	+(1)
	best with L-tube		1.3		230	200	15	60	0
6	Vapco*	6	1.52	76	287	239	29	150	+(1)
7	Broemmel	4	1.42	61	273	235	21	207	0
8	Peralta*	3	1.4	61	317	195	17	308	+(2)
9	Selrodo*	2	0.96	39	300	235	11	125	0
10	Endiphrinizer*	1	0.86		705	300	18	100	+
11	Parke-Davis "Nebulizer"*	3	0.82	67	480 (1)	drops	11	325	++(3)
12	DeVilbiss 44*								
	old type	2	0.60	59	drops	drops	10	40	0
	new type	2	0.77	61	634	432	19	75	0
13	Defender*	2	0.73	60	660	445	12	150	++(1)
						drops(1)			
14	Stearns* old type	4	0.68	47	472	367	11	87	0
	new type	2		67	575	drops	12	175	+++ (2)
15	Parke-Davis "Vaporizer"*	5	0.40	60	608	450	10	165	++(2)
						drops(2)			

\* No carburetor hole.

\*\* Values have comparative significance only.

the room temperature, the force of the blast and the viscosity and surface tension of the liquid. A number of factors will also change the size of the particles from the time they are generated until they are deposited on the respiratory mucosa. Factors which increase particle size are (1) collision of particles with each other in areas of turbulence, or by large ones overtaking the smaller; and (2) hygroscopy, if the solution has that property. Particle size may be diminished by evaporation. As previously stated, this is a function of the temperature, the relative humidity, the vapor tension of the solution, and the diameter and velocity of the particle.

After considerable experimentation with different solutions and different methods of collecting and visualizing the mist particles, the following simple technique was adopted. A small quantity of 1 per cent aqueous gentian violet solution was placed in the nebulizer and the mist sprayed against a clean glass slide held exactly one-half inch from the mouthpiece of the nebulizer. The size of the colored circular spots was then determined, using an ocular micrometer in the microscope. The median size obtained with the samples of each model was determined and the mean for the model recorded in the table. The largest droplet found with each sample was also measured and the mean for the samples for each model entered in the table. *It should be emphasized that these values have comparative significance only.* The absolute sizes are probably quite different. Many of the smaller particles evaporate before they reach the

## COMMERCIAL NEBULIZERS—HARSH

glass slide, or drift away without adhering to it. Also we cannot determine the size of the original spherical particle from the size of the flat circular spot left on the slide. A considerable amount of flattening must occur, and this amount will depend upon the momentum and size of the particle. The factors previously mentioned which tend to alter the size of the particle from the time it is generated are also operative. It should be remembered that the amount of medicament carried by particles of different sizes varies with the cubes of their radii. For example, if 99.9 per cent of the particles of a mist were 1 micron in radius and 0.1 per cent were 10 microns in radius, the mass of medicament would be equally divided between the two sizes.

### DISCUSSION

As is shown in the table, the amount of solution delivered by one compression of the hand bulb varies in the different models from 0.4 mg. to 13.0 mg. If individual samples are considered, the difference is even greater. It is therefore not a matter of indifference which model is selected. Merely to increase the number of inhalations when using the less efficient models is often not satisfactory. Even with efficient samples, many chronic asthmatics develop thick calluses on their hands from squeezing the bulb. The original workers who investigated inhalation of nebulized epinephrine in asthma quickly found that ordinary atomizers which sprayed droplets were unsatisfactory. A DeVilbiss No. 14 atomizer delivers about 100 mg. of the solution, mostly in the form of droplets, with one squeeze of the bulb, and deposits the bulk of the solution in the mouth, pharynx, and trachea. It would seem to the writer that the designers of some models of nebulizers have gone too far in trying to eliminate droplets from the spray. They have provided baffles which take out too much of the spray and in some cases, by inadequate streamlining of the instruments, have created areas of turbulence which defeat the purpose of a baffle, so that particles are actually enlarged by collision with each other. Also, to minimize clogging, they have made the capillary tube which delivers the air blast too large. This necessitates a quick, vigorous squeeze of the bulb and results in a very brief stream of mist. A more prolonged stream is a distinct advantage.

The models which deliver the greater amount of mist are preferable in nebulization of antibiotics because they reduce the time necessary for the patient to inhale the medicament. When used for this purpose, the production of droplets is not so serious as when used for inhalation of epinephrine.

By the method used in this study, no conclusion can be drawn regarding the effect of particle size on clinical efficiency. For example, two very efficient models, the Asthma Nefrin and the Vapco, are at the opposite extremes so far as the median size of the particles is concerned. It may very well be that if we could determine the percentage of medicament which is

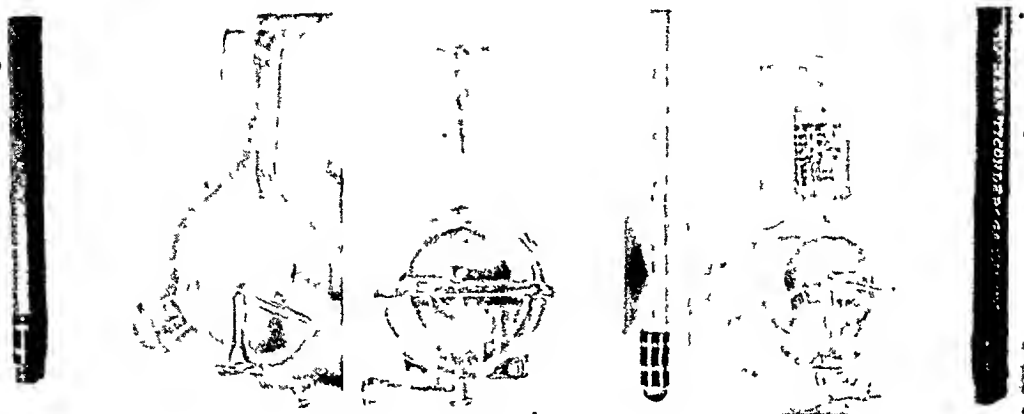


Fig. 3. Vaponefrin.

Fig. 2. Asthma Nefrin.

Fig. 1. Breatheasy.



Fig. 4. DeVilbiss No. 40.

carried by the smaller particles and exhaled, we could better explain success and failure with certain nebulizers. Also if we knew the percentage by weight of particles which are deposited in the alveoli we could better choose which nebulizers to use for local effect on the bronchi and which to use when systemic absorption is desired.

#### NEBULIZER MODELS

1. *Breatheasy* (Breatheasy Distributors, Inc., 65 Cedar Street, Seattle 1, Wash. Pyrex. \$10.00). As defined by Abramson,<sup>3</sup> instruments without baffles are atomizers. Technically, according to that definition, this model is, in part, an atomizer, since some of the mist stream passes in a straight line from the jet to the mouthpiece. However, particle sizes compare favorably with other models. The stream of mist is emitted with considerable velocity so that the larger particles lodge on the posterior pharyngeal wall (many particles were deposited on a mirror one foot away from the mouthpiece). The large volume of mist delivered may be objectionable in the hands of children and uncooperative patients. The amount of mist and the velocity of the particles may be sharply diminished by closing the carburetor hole. The larger particles may be removed nicely by the use of an L-tube such as is supplied in the DeVilbiss No. 640

combination. The Breatheasy model would seem to be the instrument of choice for such procedures as local administration of streptomycin in tuberculous laryngotracheitis. The variation in the performance of the two samples listed is chiefly due to the different capacities of the hand bulbs

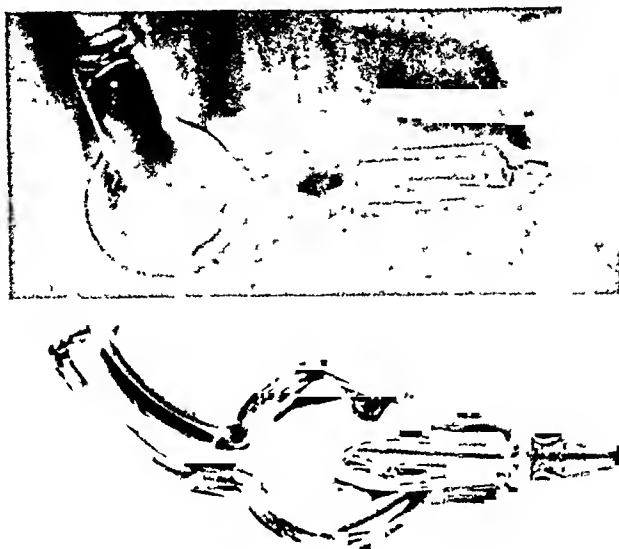


Fig. 5. Vapco.

Fig. 6. Broemmel.

supplied "as purchased." Two additional samples with the larger bulb yielded 7.0 mg. and 14.3 mg., respectively, with one compression. I have had too little experience with this model to report on clinical results with it. It gives a desirably prolonged stream with each blast.

2. *Asthma Nefrin* (Asthma Nefrin Co., 3146 E. Burnside St., Portland 15, Oregon. Plastic. \$10.00). There was little variation in the samples tested. It is very similar in design to the Vaponefrin model. It is somewhat more difficult to clean than are the glass nebulizers.

3. *Vaponefrin* (Vaponefrin Co., Upper Darby, Pa. Pyrex. \$7.50). Output in the six samples tested varied from 1.36 mg. to 2.72 mg. in one puff. Very good clinical results have been widely reported.<sup>2,3,5,16</sup> The vapor stream is gratifyingly prolonged.

4. *Pcn-i-sol*. This is sold for inhalation therapy with antibiotics, not for epinephrine therapy.

5. *DeVilbiss No. 40* (DeVilbiss Co., Toledo, Ohio, \$2.50). The output varied from 1.2 mg. to 1.84 mg. in one puff. Good clinical results have been reported.<sup>2,3,4,6</sup>

6. *Vapco* (Vaporizer Products Co., 776 Harrison St., San Francisco 7, Calif. \$2.75). The output varied from 1.12 mg. to 1.68 mg. in one puff. A fine, billowy cloud of mist is produced. This is the most efficient of

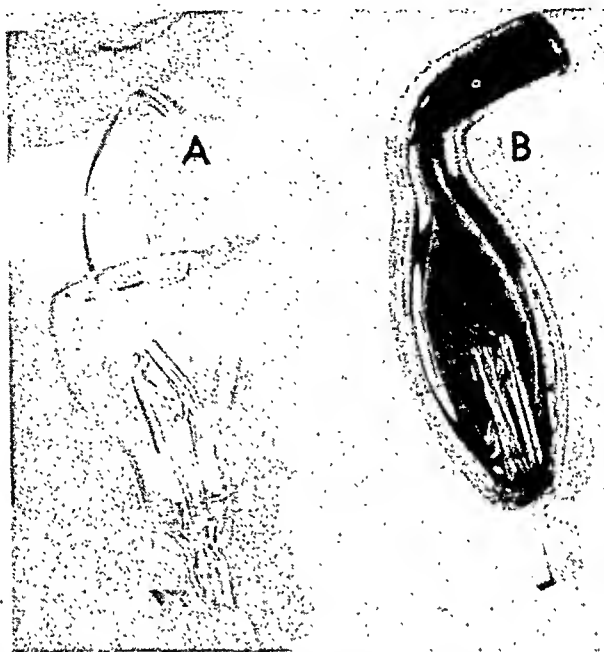


Fig. 7. (A) Peralta. (B) Selrodo.



Fig. 8. Endiphrinizer.

the models tested which have no carburetor hole; and of those which have a carburetor hole, only the Breatheasy exceeds it when operated with the hole closed. The rather large median size of the particles should be advantageous in medicating the upper part of the bronchial tree. Asthmatic patients report good results with this nebulizer.

7. *Broemmel* (Broemmels Pharmaceuticals, 384 Post Street, San Francisco, Calif. \$4.50). This is a very compact nebulizer. It produces a fine

cloud of mist. The output in four samples varied from 1.42 mg. to 1.6 mg. in one puff. It gives a prolonged vapor stream. To shorten the time in the inhalation of antibiotics, et cetera, a Y-tube may be connected to the

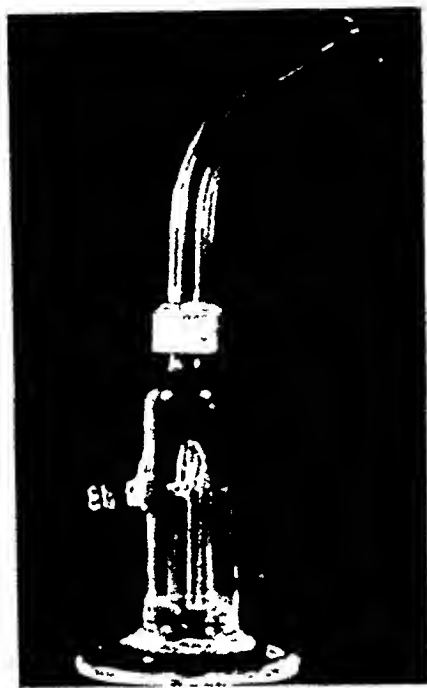


Fig. 6. Parke, Davis "Nebulizer."

tube from the oxygen tank and a pair of these nebulizers, held together by tape, may be attached to the two forks of the Y-tube.

8. *Peralta* (Peralta Hospital, Inc., 430 30th St., Oakland, Calif. Pyrex. \$2.50). The output varied from 0.8 mg. to 2.4 mg. in the four samples tested. It is constructed with a "moat" so that it will not spill if laid down. I have had too little experience with this model to report results.

9. *Seirodo* (Stansbury Chemical Co., 1929 Aurora Ave., Seattle 9, Washington. Brown glass, \$5.00). (Formerly Halomist, 705 Shafer Building, Seattle, Washington.) This was the most compact model examined. The output varied from 0.8 mg. to 1.12 mg. in one puff in four samples. Patients report good results with this model. A pair may be used as described with the Broemmel. I would prefer a larger hand bulb.

10. *Bediphrizer* (The Hartower Laboratory, Inc., Glendale, Calif. \$1.50). Only one model was tested, and I have had no clinical experience with it.

11. *Parke-Davis "Nebulizer"* (Parke, Davis & Co., Detroit, Mich. \$1.50). The output varied from 0.68 to 1.0 mg. in one puff in three

samples. Too many droplets were produced in the samples tested. Only one of the three could be used with oxygen at 8 liters per minute and none with the Selrodo air compressor. It might be improved by providing a mouthpiece of larger diameter.

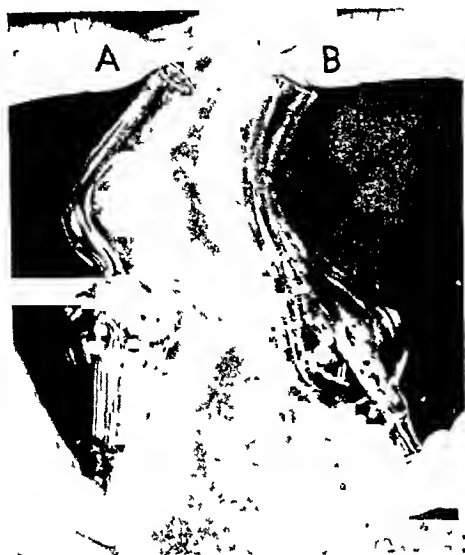


Fig. 10 (A) Defender. (B) DeVilbiss No. 44.



Fig. 11. Stearns.

12. *DeVilbiss No. 44* (DeVilbiss Company, Toledo, Ohio, \$1.50). The output of two old type models was 0.44 mg. and 0.76 mg., respectively, in one puff. The old type could not be used with oxygen at 8 liters per minute, or with the Selrodo compressor, due to emission of drops. The new type has a mouthpiece of larger diameter and was satisfactory in this respect. The output of the two new models was 0.7 mg. and 0.84 mg., respectively, in one puff.

13. *Defender* (United Drug Company [Rexal] \$1.50). This model appears to be similar to, if not identical with, the Holmspray No. 630, judging from an illustration of the latter only. The output was 0.69 mg. and 0.86 mg. per puff in the two samples. One sample emitted droplets. I have had no clinical experience with this model.

14. *Stearns* (Frederick Stearns & Co., Detroit 31, Mich. Plastic. \$1.50). In addition to hand bulb operation, this model has three inlet holes in the base which permit the patient to use the instrument without a bulb by inhaling forcibly through the mouthpiece. These holes also act as "carburetors." This method is usually effective only in mild attacks of asthma. The old type had a curved baffle plate in the dome and emitted a fine mist. The new type has no baffle plate. Furthermore, the mouthpiece tube projects into the dome and has a beveled end with the bevel turned downward so that in the two samples tested, droplets were emitted. In

the author's opinion, this model was improved when he substituted a mouthpiece of larger diameter, attached flush with the wall of the dome, and bored a  $\frac{1}{8}$  inch carburetor hole in the side.



Fig. 12. Parke, Davis "Adrenalin Vaporizer."

15. *Parke-Davis Adrenalin Vaporizer* (Parke, Davis & Co., Detroit, Mich. \$1.50). The output varied from 0.36 mg. to 0.46 mg. in one puff. It produces an almost invisible mist. The vapor stream is very brief. Two of five models emitted droplets with the hand bulb and could not be used with the Selrodo compressor. Failure to relieve asthma was very frequently reported with this model. In justice, it should be stated that this may be due in part to the probability that it outsells all others.

#### SOLUTIONS

Abramson,<sup>1</sup> in 1940, pointed out the advantage of adding to the solution to be nebulized some substance which lowers the vapor pressure. Glycerin was found to be the most satisfactory for this purpose. Concentrations of 10 to 50 per cent were used but 50 per cent was the concentration of choice. In a later communication<sup>2</sup> he lists the advantages of adding glycerin, as (1) stabilization of the mist, (2) reduction of irritation, and (3) retardation of absorption.

So far as is known to the author, only two commercial solutions and the solution adopted by the U. S. Army for the inhalation of epinephrine contain glycerin, as will be seen later.

The viscosity of aqueous solutions containing glycerin increases geometrically as the percentage of glycerin increases. Because of this increase in viscosity it is desirable to keep the percentage of glycerin at the lowest point which will accomplish stabilization of the mist. Examples of the viscosity of aqueous solutions of glycerin at 20° C. follow:

Glycerin %	Viscosity
10	1.3
25	2.1
35	3.0
50	6.0
67	18.0
75	36.5
95	540.0



For those nebulizers which produce an adequate volume of mist with distilled water, the reduction in volume when 50 per cent glycerin was substituted was not serious. Indeed, with most of them, 75 per cent glycerin could be used satisfactorily.

In addition to the advantages enumerated by Abramson, there are other reasons for the addition of glycerin: (1) the remarkable chemostatic properties of 50 per cent or more of glycerin, (2) bacteriostasis in similar concentrations, (3) prevention of clogging of the jet, and (4) the wetting effect.

Allergists are well aware that allergen extracts remain sterile and potent almost indefinitely in 50 per cent glycerin. Enzymes likewise retain their potency for prolonged periods in this medium. It seems probable that the result would be similar with antibiotics. If this is so, then even though glycerin is not necessary to stabilize penicillin mists, because of the stabilizing effect of the penicillin itself, the addition of 50 per cent glycerin would seem desirable since it would make refrigeration unnecessary.

Clogging of the jet of the nebulizer is usually due to the deposition of solid particles as the water itself evaporates. This characteristic is especially important in the nebulization of sulfonamide solutions in which 5 per cent is the usual concentration of the drug. Glycerin, since it is nonvolatile, prevents this effect.

The formulas of some commercial and noncommercial epinephrine solutions, with comments, follow:

*Breatheasy*

Racemic epinephrine HCl	3%
Benzyl alcohol	1%
Vanillin	0.2%
Sodium chloride	0.9%

The dextro-isomer of epinephrine is relatively inert. Two per cent racemic epinephrine is about 7 per cent more active than 1 per cent U.S.P. (levo-)<sup>1</sup> epinephrine. Therefore this solution is approximately equivalent to 1.6 per cent U.S.P. The benzyl alcohol is added for its local anesthetic properties and the vanillin for chemostabilization. Some patients like the strong vanilla odor, others object to it. The addition of 0.9 per cent sodium chloride to a solution containing the other diffusible ingredients makes this solution hypertonic.

*Vaponefrin*

Racemic epinephrine HCl	2.25%
"analogous to 1.5% U.S.P."	
Chlorobutanol	0.5 %

This solution is sold only through physicians. Essentially identical solutions are sold directly to the public under the names of Asthmanefrin, Solution A, Inhalant A, Neosol, Solution N, and Inhalant N.<sup>1</sup>

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## *Epinephrine inhalant*

Epinephrine (Vaporizer Products Co.)	1.0%
Chlorobutanol	0.5%
Sodium chloride	0.8%
Sodium bisulfite	0.1%
Glycerol	q. s.
Aqua destillata	q. s.

## *Adrenalin chloride* (Parke, Davis & Company) 1:100

Adrenalin HCl	1.0%
Sodium chloride	0.9%
Chloretone	0.5%
Sodium bisulfite	0.1%

## *Suprel* (formerly Nebulin A) (Frederick Stearns & Co)

Epinephrine HCl	1.0%
Alcohol	0.5%
Glycerine	7.5%
Chlorobutanol	0.5%
Sodium bisulfite	0.1%

## *Endiphrin Inhalant* (Harrower Laboratory)

Epinephrine HCl	1.0%
Sodium chloride	0.9%

## *Selrodo* (formerly Halomist)

Racemic epinephrine	1.8%
"approximately equivalent to 0.9% U.S.P."	
Chlorobutanol	0.9%

"Selrodo" spelled backwards is "odorles," but the odor of chlorobutanol is readily detectible.

## U. S. Army, Stock No 1,175,320, July 16, 1945

Epinephrine HCl	1.0%
Sodium chloride	0.9%
Glycerin	25.0%
"Suitable preservatives"	
Water	q s. 100.0%

## Typical formulas used by Abramson:

1. Epinephrine HCl 1.0%  
Chloretone 0.5%  
Sodium bisulfite 0.1%  
Water 50.0%  
Glycerine 50.0%
2. Epinephrine base 1.0%  
Chloretone 0.5%  
Sodium bisulfite 0.1%  
Water 40.0%  
Molar phosphoric acid 5.2%  
Glycerin 50.0%

## SUMMARY

1. In inhalation therapy with nebulized solutions, the choice of a nebulizer is not a matter of indifference. In fifty-nine samples representing fifteen brands of commercial nebulizers there was a 40-fold variation in the amount of solution delivered by one compression of the hand bulb. No one model was found best for all purposes.

2. Certain samples emitted droplets by hand bulb compression, and for this same reason certain ones could not be used with oxygen at 8 liters per minute or with compressed air at 40 pounds per square inch.

3. Individual models of commercial nebulizers are illustrated and discussed.

4. The formulas of certain commercial and noncommercial epinephrine solutions for inhalation therapy are given.

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# ALLERGIC RHINITIS: COMPLETE DENTAL X-RAY EXAMINATION IN SEARCH FOR DENTAL FOCI OF INFECTION

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THE role of supersensitivity to microbial antigens in clinical allergy is one of the most controversial questions of this field.<sup>1,3-6</sup> Single clinical observations can but little contribute to the solution of this problem. However, many of us have been impressed by the favorable influence of the elimination of foci of chronic infection upon allergic conditions. This is illustrated by the following case history. It seems to be worth while reporting because it emphasizes the need for a thorough search for foci of infection, which in this particular case was located only after a complete dental x-ray examination.

## CASE REPORT

The patient, a Second Lieutenant in the Chemical Warfare Service of the United States Army, was referred to the Allergy Clinic at Ft. Logan, Colorado, August 11, 1944, because of an alternating nasal blockage, mucoid rhinorrhea, and occasional sneezing.

There was no history of itching of the eyes or nose, and there were no eye complaints. These symptoms were constant and necessitated frequent visits to the Ear, Nose, and Throat Clinic. The symptoms began when the patient started work as a student in a chemical warfare service plant in Maryland in March, 1943. He stated that the weather was "cold" at the time, and his duties required his going on marches and bivouacs. From March, 1943, until October 1, 1943, the officer was transferred frequently and spent some time in Alabama, Virginia, and Miami, Florida. In October, 1943, he was transferred to Ft. Logan, Colorado. During all these moves about the country, his symptoms continued, except during the month of April, 1943, while in Alabama, where the symptoms were mild, and while in Miami, Florida, when, as a training officer working out of doors almost continuously, he was practically symptom-free. In October, 1943, after his transfer to Ft. Logan, the nasal obstruction and rhinorrhea became much more severe, and especially so starting in November, 1943. At Ft. Logan he continued his work as a Chemical Warfare Service officer. This brought him in contact with all Chemical Warfare Service materials. The patient was newly married. The patient also stated he kept a cat as a pet in his house. Inhalation of house dust in large quantities caused occasional sneezing but no real difficulty. His history revealed no relation to foods. It was noted that the patient was worse during the day and that the complaints did not keep the patient up at night. He also stated that he was definitely worse indoors. After nasal polypectomy in January and again in August, 1944, the symptoms were partially relieved for about one week each time.

*Family History.*—Negative for allergic diseases.

*Past History.*—

Medical: Irrelevant.

Surgical: Nasal polypectomy in January, 1944, and again in August, 1944. Tonsillectomy and adenoidectomy at the age of nine years.

Injuries: In 1938 he fell on his face, thereby breaking a tooth and lacerating his chin and lip. At the time he was dazed, but not unconscious.

Venereal Disease: Denied.

Social history: Married since April, 1943. He smoked a pipe occasionally.

*Physical Examination.*—He was a well-nourished and well-developed twenty-three-year-old white man who did not appear acutely or chronically ill. Head and eyes: slight conjunctival injection. Ears: normal external auditory canal; tympanic membranes normal. Nose: the left inferior turbinate was pale, and polyps were seen. Pharynx: essentially negative. The remainder of the physical examination, including neck, heart, lungs, abdomen, extremities and lymph glands, revealed no pathological findings.

*Laboratory Data.*—

1. Oral dental examination revealed the patient to be in Class IV, normal.

2. On October 28, 1944, x-ray of the sinuses showed changes of both maxillary sinuses suggestive of hypertrophic sinusitis. An x-ray of the sinuses taken May 4, 1944, revealed some clouding of the right maxillary antrum and slight clouding of the frontal sinuses. The other sinuses appeared clear.

3. Pathological report of nasal polyps removed in August, 1944: Gross—Specimen consists of two disc-shaped pieces of pearl white edematous tissue, 0.8 by 0.3 cm., and 0.66 by 0.2 cm. Microscopic—Numerous eosinophiles.

4. Dental consultation with full dental x-rays revealed a periapical abscess of the upper right lateral incisor.

5. Allergy tests: Intradermal tests—House dust gave a 1+ reaction to 100 PNU, 2+ to 1,000 PNU, and 3+ to 10,000 PNU. There were 2+ reactions to white potato, apple, and tobacco 1-10, lemon gave a 1+ reaction. Cat ep, dog ep, rabbit ep, feathers, cottonseed, flaxseed, kapok, silk, pyrethrum, fish glue, orris, human dander, egg white, milk, wheat, beef, chicken, pork, fish, cornmeal, lima bean, orange, mustard, green pea, banana, chocolate, peanuts, barley, rye, buckwheat, asparagus, beets, cabbage, carrot, celery, sweet corn, shrimp, grape, grapefruit, peach, and pineapple were all negative. The molds *Alternaria*, *Aspergillus*, *Horodendrum*, *Helminthosporium*, *Spondylocadium*, *Penicillium*, and *Fusarium*, were essentially negative on testing to extracts of 1,000 PNU per c.c. with readings at twenty minutes, twenty-four hours, and forty-eight hours. The following pollens were tested in 100 PNU, 1,000 PNU, and 10,000 PNU strengths and were all found essentially negative: timothy, plantain, ragweed, ash, beech, birch, elm, hickory, oak, sycamore, carelessweed, lamb's-quarters, Russian thistle, redroot pigweed, sagebrush, and summer cypress. Patch tests to shaving cream (Burma Shave), face powder, activated charcoal, lipstick, cold cream, rouge, hand lotion (Jergens), talc and zinc hexachlorethane were all negative; readings were made after forty-eight hours with the patches in place and again in forty-eight hours after the patches were removed. Inhalation tests by having the patient inhale through his nose small amounts of the following substances gave no change in the subjective or objective nasal complaints: Jergens' lotion, face powder, Woodhue, talc (stored in the Chemical Warfare Warehouse), activated charcoal and soda lime, Burma Shave, lipstick, rouge, and zinc hexachlorethane.

Unfortunately, the blood picture in this case is not available, and no bacterial examination of the apical abscess was made.

*Course.*—On August 29, 1944, the abscessed tooth was removed and in about four days all nasal symptoms except for slight and occasional nasal blockage disappeared. He needed no nasal treatment from the latter part of August, 1944, until last seen in March, 1945. There was as yet no recurrence of symptoms. This was the first time since March, 1943, that this patient had had such marked and prolonged relief. This improvement occurred in spite of the fact that this patient continued at the same job.

## DISCUSSION

It appears that this patient had an allergic rhinitis, as proved by the definitely pale nasal mucosa with watery rhinorrhea and by the pathological examination of the nasal polyp showing numerous eosinophiles on microscopic examination. He was found to have an abscessed tooth which remained unrecognized on routine oral dental examination and was only found after a full dental x-ray examination. Following removal of the abscessed tooth, remission occurred.

From a practical standpoint, this case shows that in the search for a focus of infection in the teeth, it is essential to have a complete x-ray examination of the teeth, with a careful interpretation, before one can be sure that such an infection does not exist.

The sequence of events is suggestive of a causal connection between the dental focus and the allergic condition of the nose. Different explanations of our experience—as, for instance, a nonspecific influence of the elimination of infective foci—cannot be excluded. It is well to realize that a single experience like the one reported here can be no more than a building stone for the establishment of evidence.

## SUMMARY

1. A case of allergic rhinitis is reported in which removal of an abscessed tooth was followed by a remission.
2. The focus of infection in the tooth was found only on complete x-ray examination of the teeth.
3. It is suggested that complete dental x-ray examinations are useful in the search for foci of infection.

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Instead of crying, "Can we afford some new service?", we are now tending to realize that we cannot afford ill-health and the resulting loss of productive work. We are beginning to realize that expenditure on preventive services and on health research pays an enormous dividend.—SIR ANDREW DAVIDSON, *British Medical Journal*, Feb. 7, 1948.

## MULTIPLE SCLEROSIS—TREATMENT WITH HISTAMINE AND d-TUBOCURARINE

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MULTIPLE sclerosis is a disease of the central nervous system characterized by exacerbations and remissions. It has long been recognized that the early symptoms of multiple sclerosis are often mistaken for hysteria. There appear to be several reasons for this error. The first complaints often seem bizarre, and only few objective abnormal findings can be demonstrated on careful examination. The symptoms frequently disappear spontaneously. Thus it comes about that individuals who have a number of attacks of transient numbness or paralysis, later show definite signs of organic disease of the nervous system. Approximately one patient in twelve with the disease may be expected to require institutional psychiatric help at some time.<sup>18</sup> In 1836 or 1837 Sir Robert Carswell<sup>16</sup> described a pathological specimen of the pons and cord spotted with grey areas of atrophy. About thirty years later Charcot gave a review of the literature and named the disease.

There are multiple patches of sclerosis scattered diffusely throughout both the grey and the white matter of the cerebrospinal axis.<sup>3</sup> These are areas of glial overgrowth in which the nerve fibres are usually preserved, at least to the extent that the axis-cylinders pass through but are deprived of their myelin sheaths.<sup>19</sup> Careful studies of the degree of destruction within the plaques have given conflicting results. Putman,<sup>23</sup> on the one hand, states that in a little more than 50 per cent of the plaques there is complete or almost complete loss of nerve fibers; Greenfield and King,<sup>9</sup> on the other hand, report that in less than 10 per cent is there severe destruction, and that in the remaining, little or no diminution in the number of axis-cylinders is found. This divergence is probably to be explained by the difference in technique employed. It is this persistence of conducting elements that accounts for the absence of tract degenerations in multiple sclerosis.

The three types of the disease are acute, remittent and the chronic progressive. The remittent may become chronic progressive. Prognosis depends on the type. It is very poor for the acute rapidly progressive, and good for the other types. A hopeless prognosis should not be made.<sup>27</sup> As Von Hoesslin<sup>33</sup> pointed out, the prognosis in cases of multiple sclerosis may by no means be as hopeless as many textbooks would lead one to believe. Substantial remissions, so complete that the patients considered themselves practically well, occurred in 17 per cent of his cases. About 70 per cent of cases appear between the ages of twenty and forty

Presented at the fourth annual meeting of the American College of Allergists, March 12-14, 1948.

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years. Less than 2 per cent occur before the age of ten, and 4 per cent after the age of fifty.<sup>2</sup>

Scheinber<sup>26</sup> expressed the view that the acute and the chronic forms of multiple sclerosis are varieties of the same morbid entity. The structural differences in the lesions are explained by the difference in intensity and duration of the same morbid process. There are many theories as to the cause of the disease, among them being that multiple sclerosis is the result of allergies. In 1938 Kennedy<sup>17</sup> and Pardee<sup>22</sup> among others called attention to allergic reactions in the central nervous system, Kennedy pointing out the possibility that multiple sclerosis is the result of allergy. Of this Carter<sup>5</sup> says: "The short and transitory remissions and exacerbations of symptoms can be readily thought of as being due to transitory allergic tissue edema which interrupts function of the central nervous system temporarily, and that permanent loss of function comes only after prolonged or repeated episodes of tissue hypersensitivity."

Earlier, A. Ferraro<sup>7</sup> said: "The pathologic syndrome of all demyelinating diseases appears plausible as the expression of an allergic reaction or nerve tissue. With this conception of a common cause applied to many seemingly unrelated clinical entities, we have used histamine as a therapeutic agent with marked success in many subjects."

Shortly thereafter, Horton,<sup>10,14</sup> Sollman,<sup>29</sup> MacLean and Craig,<sup>14</sup> Shelden,<sup>28</sup> Rainey,<sup>24</sup> Thomas and Butler,<sup>32</sup> Brown,<sup>13</sup> Roth,<sup>13,25</sup> Rynearson,<sup>25</sup> Alexander and Elliott,<sup>1</sup> Christian<sup>6</sup> and many others reported the successful treatment of many neuroallergies with histamine. In 1943 Horton and his co-workers Wagener, Woltman and Woltman<sup>15</sup> reported the treatment of 102 cases of multiple sclerosis with the daily intravenous administration of 2.75 mg. of histamine diphosphate in 250 c.c. of isotonic solution of sodium chloride. This report indicated varying degrees of improvement in over 50 per cent of the cases.

Following this report, we began the use of histamine diphosphate both intravenously and subcutaneously in different neuroallergies including multiple sclerosis. For more than two years we have been using histamine diphosphate in the treatment of multiple sclerosis, first using prostigmine combined with histamine, and later d-Tubocurarine, with muscle re-education and allergy management. During this time, we have treated 124 cases, seventy-five females and forty-nine males. The reason for this divergency by sexes is probably economic. The wife with multiple sclerosis is able to come and be treated. On the other hand, should the husband be the victim of the disease, it is difficult financially for him to leave home to take treatment. Practically all of our cases have been of the chronic progressive type; only six could be classified as acute. Age is a major factor in the disease, the vast majority of the cases having their first attack between twenty and forty. The average age of onset in our series for females was 29.16 years, and for males, 30.41 years. The oldest at onset was forty-nine for males and forty-nine for



females. The youngest onset in our series was fifteen for females and twenty for males. The average duration of the disease for females was 9.48 years, and for males, 11.34 years.

All of our patients came to us with a definite diagnosis of multiple sclerosis made at a recognized neurological clinic or by a reputable neurologist. Those that came with the diagnosis made under other circumstances, were referred to competent neurologists for a thorough neurological examination and report. We were not responsible for the diagnosis of multiple sclerosis in any case, although we concurred in the diagnosis of multiple sclerosis before starting treatment.

#### SYMPTOMS

The most marked symptom that was noted in our cases was that of weakness and exhaustion on effort. Practically all complained of this condition at one time or another. Nystagmus was present in most of the cases, with diminished abdominal reflexes, while the deeper reflexes of the lower extremities were markedly exaggerated in most patients. Bladder symptoms, speech hesitancy and gait disturbances were present in about half of the patients. Tremors and emotional instability with personality changes were also present in about one-half of our patients. Visual impairment with a history of diplopia and optic neuritis occurred in a large percentage of the cases. About half of our patients were bedfast or confined to wheel chairs. In some, tremors and spasticities were so violent that it was necessary to use restraining sheets at first. These latter cases responded to treatment rapidly and very satisfactorily. About 20 per cent suffered from pain in varying degrees, which also responded quickly in the majority of our cases. Sixty-three suffered from quadriplegia, paraplegia or hemiplegia.

In multiple sclerosis, spasticity is one of the principle disabling factors; therefore, if the spastic condition can be relieved and the tremors controlled, the patient may become a useful worker again. Nearly all of the cases of multiple sclerosis were of the chronic progressive type, most of them being very spastic. To help control this spastic condition and the intention tremors, we were of the opinion that curare would be the best drug. The problem was to find a preparation that could be given in sufficiently large doses to control spasticity and tremors and still be safe. Bernard<sup>4</sup> had shown that curare causes an elective release of rigidity in spastic muscles while the normal musculature was unaltered. This release may be enough to convert a hand which is entirely useless into one in which active co-ordinate motion can be accomplished. While curare will not convert a paralyzed muscle into an active one, the release of the rigidity may allow a muscle not completely paralyzed to begin functioning actively. Curare produces its effect by an elective affinity for the hyperinnervated myoneural junction. It is also an autonomic

blocking agent active mainly on skeletal muscles and to a lesser degree on autonomic ganglia.<sup>8</sup> It does not paralyze smooth muscle.<sup>20</sup>

#### D-TUBOCURARINE

d-Tubocurarine is the most effective and stable of the various curare alkaloids. We found that d-Tubocurarine in the aqueous solution was too fleeting in its action to be of any value. Prolonged action was necessary to permit any activity on the part of the patient. A suspension of d-Tubocurarine made according to the formula of Schlesinger,<sup>27</sup> and containing 30 mg. per c.c. of d-Tubocurarine in a base composed of 4.8 per cent white bees-wax in peanut oil,<sup>2</sup> was used. This was given deep into the muscle in doses that varied from 7.5 mg. every fourth day up to as much as 120 mg. daily. There was a wide range in dosage among patients, the effects in some lasting as long as ninety-six hours, in others only twelve to sixteen hours.

The action of the d-Tubocurarine in oil and wax was startlingly good. This preparation gave prolonged action with constant effects. It gave an immediate feeling of relaxation and comfort to the tense, spastic patients. The first dose often gave them the first comfortable night's sleep they had had in years. Incontinence and frequency of urination were improved or controlled in a very short time in every case. Constipation, the "bugaboo" of multiple sclerosis, was relieved in most patients within a few weeks. Tremors were markedly reduced in all cases. Voluntary movements previously blocked by spastic rigidity were made possible and patients were able to move hands, arms, legs and other parts of their body in varying degrees approaching normal. These limbs had previously been paralyzed or uncontrollable through spasticity and tremors.

Following the prolonged use of d-Tubocurarine, there appeared an accumulative action with the development of an increased sensitivity to its action. Smaller doses could then be given at increased intervals with constant effect. Some patients were able to go for a month to six weeks without a noticeable return of tremors, muscle rigidity or spasticity. Because of this, patients were able to take vacations from treatment at varying intervals with a good effect on their morale.

We have given over 20,000 doses of d-Tubocurarine in the last eight months without a single undesirable reaction. Neither has there been any tendency to habituation in any case. As a matter of fact, the patients all seem to want to decrease their dose as rapidly as possible. This is because the accumulative effect is prone to produce uncomfortable dizziness, slight visual symptoms or other side effects, unless the amount of the drug given is gradually decreased. Also, at certain times after the drug has been administered over a period, there will develop a "stiffness" or lack of power in all four limbs and lower jaw. This condition is relieved by withdrawal of the drug for a week or ten days.

\*Supplied through the courtesy of the Abbott Research Laboratories.

# MULTIPLE SCLEROSIS—JONEZ

TABLE I. FORTY CHRONIC PROGRESSIVE MULTIPLE SCLEROSIS CASES  
Treated at St. Joseph's Hospital, Tacoma, Wash., Nov. 15, 1947 to Feb. 15, 1948

Case No. Age Occupation	Surgery Trauma Accidents	Allergies	Attacks Type	Previous Treatment Results	Symptoms on Admission	Histamine Diphosphate	d-Tubo- Curarine In Oil and Wax	Present Condition
1. Mr. M. W. 60. Yeastmaker.	None.	Rhinitis. Foods. Molds.	1925 Ch. Prog.	None.	Urinary Incontinence. Spastic Paraplegia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Urinary incontinence stopped. Paraplegia improved.
2. Mrs. L. A. 49. H. W.	None.	Hives. Foods.	1933 Ch. Prog.	Small amount of Histamine once weekly for six weeks.	Spastic Paraplegia. Paresis. Dysarthria. Pollakiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	22.5 mg. 3 times weekly.	Spastic Paraplegia improved. Walking. Dysarthria im- proved. Pollakiuria improved. Amblyopia improved.
3. Miss G. S. 43. Telephone Operator.	Fractured right leg 1915. Appen- dectomy. Double mastoid.	Rhinitis. Ecze- ma in child. Food. Epidermals.	1941 Cr. Prog.	Fever therapy Improved.	Amblyopia. Hippius. Spastic Paresis all 4 limbs. Pollakiuria. Cane case.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Amblyopia. Hippius and Polla- kiuria all marked improvement. Spastic paresis entirely con- trolled. Does not use cane at all.
4. Mrs. M. P. 40. H. W.	None	Many foods.	1932 Ch. Prog.	None.	Spastic Quadriplegia. Dysphasia Oscillopsia. Complete incon- tinence. Retention catheter. Bed-fast 13 years.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. daily.	Homesick. Left hospital after six weeks. No improvement.
5. Miss G. M. 25. Telephone Operator.	Pelvic lap. 1916. Stung by "yellow jacket" 1938. 2 weeks later 1st symptoms.	Rhinitis Neuroderma.	1939, 1941 Remittent. 1947 Ch. Prog.	Histamine I.V. daily 3 mos. 14 Prostigmine 14 injections daily. Worse.	Dysphasia. Dysphasia. Spastic Quadriplegia. Oscillopsia. Left external Strabismus. Pollakiu- ria. Left amaurosis. Bed-fast 6 mos.	2.75 mg. daily for 10 days, then 3 times weekly.	60 mg. daily.	Dysphasia improved. Dyspha- sia slight improvement. Spastic Quadriplegia marked improve- ment. Strabismus improved. Pollakiuria entirely relieved. Left amaurosis improved. In wheel chair.
6. Mr. K. B. 36. Sailor.	Appendectomy 1936.	Colds. Foods.	1938, 1939 Remittent. 1940 Ch. Prog.	None.	Dysarthria. Dysphasia. Pares- thesis. Spastic Quadriplegia. Ophthalmoplegia. Diplopia. Pollakiuria. Amblyopia. Partially bed-fast.	2.75 mg. daily for 10 days, then 3 times weekly.	120 mg. daily.	All symptoms improved.
7. Mrs. L. F. 28. Bakery clerk.	None.	Foods.	Emotional family upset June '40. With- in 2 weeks left leg paralyzed. 1940, 1941 Re- mittent. 1941 Ch. Prog.	None.	Dysphasia. Dysphasia. Decub- itus. Spastic Quadriplegia. Hippius. Bed-fast four years.	2.75 mg. daily for 10 days, then 3 times weekly.	60 mg. daily.	Some improvement of all symptoms.
8. Mrs. F. C. 34. H. W.	None.	Foods. Pollens Epidermals.	1937, 1938 Re- mittent. 1939 Ch. Prog.	None.	Dysarthria. Spastic Quadriple- gia. Oscillopsia. Hippius. Bi- lateral External Strabismus. Euphoria. Highly emotional. Wheel chair. Urinary Incontinence.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Slight improvement some symptoms.

TABLE I. (Continued)

9. Mrs. L. C. 42. H. W.	Noac.	Foods, Epithelials.	1930 Ch. Prog.	None.	Paraplegia. Pollakiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Pollakiuria and Amblyopia unimproved. Paraplegia unimproved.
10. Mr. L. B. 48. Barber.	Appendectomy 1922.	Foods. Human hair.	1938 Ch. Prog.	Prostinine. No results.	Spastic paraplegia. Came away 3 cars.	2.75 mg. daily after 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Walks without cane and did so after first injection of d-Tubocurarine.
11. Mrs. M. B. 28. H. W.	None.	Eczema all life. Molds. Pollens. Foods.	1938, 1910 Re-nitent. 1911 Ch. Prog.	Histamine. Improved.	Euphoria. Dysarthria. Marked spastic condition, all 4 limbs. Paraplegia. Oscillopsia. Pollakiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Marked improvement of all symptoms.
12. Mrs. K. E. 31. H. W.	Cesarean section Cervical sympathectomy. Sub-mucous resections.	Rhinitis. Hay fever. Eczema. Foods.	1911. Ch. Prog.	Sympathectomy.	Very spastic. Paralysis left arm and left leg. Oscillopsia. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	In Oil and wax. 30 mg. daily.	Spastic condition so improved after 10 days' treatment that patient was able to take a 3,000 mile automobile trip. Husband giving her 30 mg. of d-Tubocurarine daily.
13. Mrs. L. E. 32. H. W.	Thyroidectomy 1936. Appendectomy 1943. T. & A. 1945.	Foods.	1915 Ch. Prog.	Histamine. 30 doses. Improved condition.	Dysarthria. Urinary incontinence. Oscillopsia. Amblyopia. Diplopia. Very spastic Paraplegia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. daily.	All symptoms improved. Incontinence relieved after first dose of d-Tubocurarine. Walks with some help.
14. Mr. F. G. 40. Steam Engineer.	None.	Foods.	1912 Ch. Prog.	None.	Urinary incontinence. Paralysis and Spastic paresis of both lower extremities.	Continuous as his time will permit up to 8 mg. in 8,000 cc normal saline during 48 hours.	30 mg. 3 times weekly.	Incontinence stopped after first dose of d-Tubocurarine. All other symptoms improved.
15. Mr. E. F. 33. Milk dealer.	Fractured ankle 1940.	Foods. Molds.	1941, 1943 Re-nitent. 1913 Ch. Prog.	1943 had 12 fever "shots." Improved. 17 one month Di-cumeral treatment. No improvement.	Dysarthria. Oscillopsia. Diplopia. Paraplegia. Pollakiuria. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Pollakiuria marked improvement. All symptoms improved.
16. Mr. J. W. 38. Office Worker.	None, and none recommended.	Foods. Hay fever. Asthma.	Ch. Prog. 1911	None.	Spastic Paraplegia. Parasthesia. Pollakiuria. Wheel chair.	Continuous as indicated up to 14 mg. in 1,000 cc normal saline during 48 hours.	30 mg. 3 times weekly.	Pollakiuria relieved after first injection of d-Tubocurarine. Other symptoms improved.
17. Mrs. E. S. 43. Reg. Nurse.	None.	Foods. Molds. Brother and sister, asthma and hay fever.	1919, 1944 Re-nitent. 1914 Ch. Prog.	23 Histamine L. V. injections. No improvement.	Spastic Paraplegia. Oscillopsia. Pollakiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Pollakiuria relieved entirely; all other symptoms markedly improved. Walking with help now.

TABLE I. (Continued)

Case No. Age Occupation	Surgery Trauma Accidents	Allergies	Attacks Type	Previous Treatment Results	Symptoms on Admission	Histamine Diphosphate	d-Tubo- Curarine In Oil and Wax	Present Condition
18. Mrs. D. H. 35. Stenographer.	None.	Hives. Eczema.	1940, 1944 Re- mittent. 1944 Ch. Prog.	1944, 40 injec- tions Hista- mine. Improved.	Dysarthria. Spastic Paralysis both lower extremities.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
19. Mr. E. A. 32. Truck Driver.	Appendectomy 1943.	Rhinitis.	1945, 1947 Re- mittent. 1947 Ch. Prog.	None.	Diplopia. Amblyopia. Polla- kiuria. Spastic Paralysis, both lower extremities.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms slightly improved.
20. Mr. G. K. 54. Meat Cutter.	Left inguinal her- nia 1943. Right inguinal hernia and appendec- tomy 1947.	Eczema. Rhinitis.	1943 Ch. Prog. immediately after operation.	Histamine 30 I. V. 2.75 mg. daily. Improved.	Dysarthria. Parasthesia. Hip- pus. Pollakiuria. Spastic paralysis both lower extremities. Anurosis.	2.75 mg. daily.	30 mg. daily.	All symptoms markedly improved.
21. Mr. R. A. W. 47. Farmer.	None.	Food.	1935 Ch. Prog.	None.	Diplopia. Anurosis. Urinary incontinence. Dysarthria. Spastic paralysis, both lower extremities.	2.75 mg. daily.	30 mg. daily.	Incontinence stopped. Other symptoms improved.
22. Mrs. G. L. 41. H. W.	Adhesion of dor- sal spinal cord loosened 1939.	Hay Fever. Asthma. Eczema.	1936 Ch. Prog.	None.	Spastic paraplegia. Dysarthria Urinary incontinence. Ambly- opia. Oscillopsia. Wheel chair.	2.75 mg. daily.	30 mg. daily.	Urinary incontinence stopped. All other symptoms improved.
23. Mr. N. S. 52. Hydroelectric Worker.	Sympathectomy 1935.	Foods. Molds.	1928, 1930 Re- mittent. 1932 Ch. Prog.	Sympath- ectomy.	Left spastic hemiplegia. Pollakiuria.	2.75 mg. daily.	15 mg. daily.	Improved.
24. Mrs. M. W. 27. H. W.	Tubal pregnancy operation April 15, 1946. One week later M. S. developed.	Foods. Molds.	Ch. Prog. 1946. immediately after operation.	None.	Dysarthria. Spastic paresis both lower extremities. Pollakiuria.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
25. Mr. G. F. 35. Salesman.	Fractured right ankle 1938.	None.	1935 Ch. Prog.	Prostigmine. 6 mos. No results.	Dysphagia. Spastic. Quadri- plegia. Dysphasia. Decubitis. Urinary incontinence. Anurosis. Bed-fast.	5.50 mg. daily.	60 mg. daily.	Up in wheel chair. A few steps. All symptoms markedly improved.
26. Mr. R. E. 42. Druggist.	None.	None.	1941 Ch. Prog.	None.	Incontinence of urine. Hippus. Dysarthria. Spastic paresis, both lower extremities.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Incontinence stopped. All other symptoms markedly improved.
27. Mr. A. Z. 45. Sawmill worker.	Appendectomy 1918. Head in- jury 1938.	None.	1938 Ch. Prog. immediately following head injury.	None.	Dysphagia. Hippus. Dysphasia. Spastic paraplegia. Pollakiuria. Anurosis. Euphoria. Bed- fast.	5.50 mg. daily.	30 mg. daily.	Up in wheel chair. Walks a few steps. All symptoms improved.

TABLE I. (Continued)

28. Mrs. H. A. 30. Bookkeeper.	Caesarian section 1942. Appendectomy 1937.	None.	1938, 1941 Re-mittent, 1941 Ch. Prog.	Prostigmine for 1 yr. No improvement.	Dysarthria. Spastic paraplegia. Oscillopsia. Diplopia. Pollakiuria.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Generally improved.
29. Mr. O. R. 33. Automobile Mechanic.	Industrial accident Aug. 1937. Right ankle injured.	None.	Aug. 1937 Ch. Prog. since ac-cident.	Quinine, 3 mos. No result.	Spastic paraplegia. Pollakiuria. Parasthesia. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Walks a few steps. All symptoms improved.
30. Mr. W.M.B. 28. Salesman	None.	Molds.	1943 Ch. Prog.	None.	Spastic paresis both lower extremities. Parasthesia. Pollakiuria.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
31. Mrs. A. R. 52. H. W.	Pelvic lap. 1942. Total hysterectomy 1942.	Hay fever.	1945, 1946 Re-mittent, 1946 Ch. Prog.	None.	Spastic left hemiplegia. Dysarthria. Parasthesia. Pollakiuria. Bed-fast.	5.50 mg. daily.	60 mg. daily.	In wheel chair. Walks a few steps. Marked general improvement.
32. Mr. I. M. P. 54. General Laborer.	Sinus 1934. Prostatectomy 1943.	Rhinitis.	1931 Ch. Prog.	None.	Spastic paresis both lower extremities. Oscillopsia. Pollakiuria. Dysarthria. Amblyopia.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
33. Mrs. E. R. 42. School Teacher.	None.	Eczema since 3 months old.	1946, 1947 Re-mittent, 1947 Ch. Prog.	None.	Dysarthria. Oscillopsia. Pollakiuria. Spastic paresis all four limbs. Euphoria.	5.50 mg. daily.	30 mg. daily.	All symptoms improved.
34. Mrs. D. G. 43. H. W.	None.	Pollens.	1946 Ch. Prog.	None.	Pollakiuria. Parasthesia. Dysarthria.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
35. Mrs. V. K. 25. H. W.	None.	Fooda. Epidermala.	1939, 1947 Re-mittent, 1947 Ch. Prog.	None.	Parasthesia. Spastic Paresis all four limbs.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Improved.
36. Mr. R.B.D. 43. Sheet Metal Worker.	None.	Asthma.	1944 Ch. Prog.	None.	Parasthesia. Pollakiuria. Amblyopia. Spastic Paresis both lower extremities.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Pollakiuria improved.
37. Mr. L.H.H. 48. Grocer.	Appendectomy 1928. Double inguinal Herniotomy 1917.	Asthma 1926 to 1936.	1936 Ch. Prog.	40 injections I. V. Histamine. No improvement.	Spastic paraplegia. Pollakiuria. Amblyopia. Dysarthria.	5.50 mg. daily.	30 mg. daily.	All symptoms improved.
38. Miss L. W. 35. Stenographer	Spinal tumor fibroids Sept. 1943. Pelvic lap. Oct. 1943. Bladder operation Jan. 1945.	Pollens. Epidermala.	1943 Ch. Prog.	None.	Amblyopia. Dysarthria. Parasthesia. Urinary incontinence.	2.75 to 11 mg. daily.	15 mg. daily.	Generally improved.

TABLE I. (Concluded)

Case No. Age Occupation	Surgery Trauma Accidents	Allergies	Attacks Type	Previous Treatment Results	Symptoms on Admission	Histamine Diphosphate	d-Tubo- Curarine In Oil and Wax	Present Condition
33. Mrs. W. S. 47. H.W.	Cervical dorsal sympathectomy for multiple sclerosis, 1941.	Rhinitis.	1926, 1937. 1938 Remit- tent, 1939 Ch. Prog.	Sympath- ectomy 1941.	Spastic paraplegia. Paresthesia. Pollakiuria. Amblyopia.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Unchanged.
10. Miss F.L.K. 58. School Teacher.	Left mastoid operation 1930.	Eczema until age 15. Hay fever.	1926, 1929 Re- mittent, 1930 Ch. Prog.	Quinine 2 weeks. Fowlers solution 2 weeks. No re- sults. Hista- mine 25 injec- tions, im- proved.	Spastic paresis both lower ex- tremities. Pollakiuria. Dysarthria.	2.75 mg. daily.	30 mg. daily.	Generally improved.

AGE SUMMARY

No.	Oldest Now	Oldest At Onset	Youngest Now	Youngest At Onset	Longest Duration	Shortest Duration	Average Age now	Average Age Onset	Average Duration
Female	22	53	25	15	23	2	38 3	27 5	10 8
Male	18	60	23	22	23	3	42 7	32 1	10 6

## PHYSICAL THERAPY

In conjunction with d-Tubocurarine, we use physical therapy, depending upon muscle re-education and hot packs. Both of these measures are used in the same manner as in the treatment of the residuals of poliomyelitis. The d-Tubocurarine so relieves the spastic conditions that when voluntary impulses get by the myoneural junction, muscle re-education is needed for the proper control of the affected limb. The hot poliomyelitis packs are of marked value in helping to break down contractures. We are able to get rigid, badly contracted limbs straightened out with the assistance of these hot packs, where, as in some cases, it is difficult to do so with d-Tubocurarine alone. Massage, either heavy or light, is not used by us, as it seems to aggravate all spastic conditions. Mild exercises are encouraged. However, we insist on all of the multiple sclerosis patients taking as much rest as possible; and those that are working are told to curtail all outside activities that are tiring.

## ALLERGY MANAGEMENT

All patients are tested for their sensitivity to foods, epidermals, molds, fungi, pollens and miscellaneous allergens. The proper diets from an allergy standpoint are prescribed, and they are all given an allergenic extract. The extracts are made using histamine diphosphate in normal saline, .275 mg. per c.c. as a base. This is injected subcutaneously in increasing doses in the same manner that histamine is given. Following the release from active treatment, the extract can be self-administered as a prophylaxis against exacerbations of multiple sclerosis.

## HISTAMINE

Our entire study was based on the theory that allergy is the etiological cause of multiple sclerosis. Therefore, our patients are given histamine diphosphate intravenously to the point of tolerance. Some received 2.75 mg. histamine diphosphate in 250 c.c. normal saline daily and others a continuous infusion<sup>30</sup> of 11 mg. histamine diphosphate in 1,000 c.c. of normal saline at a rate of 30 drops per minute, every six hours, alternating with 11 mg. histamine diphosphate in 1,000 c.c. of 5 per cent glucose solution. This continuous infusion would be given for periods of twenty-four, and in some cases forty-eight, hours. Our best results were in the cases that were able to take the larger amounts. In the cases where histamine had been a failure before coming to us, we believe that too little had been given for too short a time. A number of these patients when given larger amounts responded very satisfactorily. In the cases where only small doses of histamine diphosphate were tolerated, we gave glucophylline (theophylline<sup>31</sup>) with the idea of prolonging vasodilatation. Using histamine, we accomplished two purposes: first, the hyposensitization of the patient to the histamine reactions of allergy; and, second,



the benefit derived from histamine as a vasodilator, being the most effective vasodilator known on the tissues of the central nervous system.

In our series we have administered histamine diphosphate intravenously over 10,000 times and have had no noticeable reactions. A number of our patients have come to us with histories of reactions when histamine had been given to them previously. However, they did not have these reactions when given histamine in our clinic. We are of the opinion there are two reasons for this. When intravenous histamine is given too rapidly, reactions are bound to occur. There is also the pyrogenic factor as in all intravenous medication. This may explain some of the reactions as being the result of the improper sterilization of glassware or rubber tubing. We never administer histamine diphosphate intravenously any faster than 2.75 mg. histamine diphosphate in 250 c.c. of normal saline, or in 250 c.c. of a 5 per cent glucose solution, in less than one hour and thirty minutes.

#### CLIMATE

We noticed that all of our spastic patients exhibit more rigidity on cold days, and that all were better when the weather was warmer. A number of writers have spoken of this before.<sup>31</sup> Another symptom that cold weather seemed to produce, and which appeared to have a marked effect on the disease, was a typical "cold in the head." A majority of multiple sclerosis patients mentioned this. Patients would have several of these "colds" each year, and following each attack, the symptoms of multiple sclerosis would be worse. "Colds" appeared to be much more prevalent during the winter months when the days were short. Attacks of sinusitis and rhinitis undoubtedly play a major role in some way in bringing on exacerbations and intensifying symptoms. This undoubtedly explains in a way why multiple sclerosis is looked upon as a disease of the colder climates, and why a great many of these cases improve when they go to a warm dry climate. In all the inquiries to us regarding treatment, there were practically none from the southern half of the United States. The majority of inquiries outside of the states of Washington, Oregon and Idaho came from Montana, Minnesota, Michigan, the Dakotas and Canada. In our entire series, we had only two patients from California; one from near Oakland and one from near Los Angeles. Several of our patients, following treatment with us, went to Southern California and Arizona and continued to improve while spending the winter months in the South.

#### SUMMARY AND COMMENTS

Summarizing our 124 cases, we find that nearly all had some form of allergic sensitivity. Those with multiple food sensitivities apparently were, as a general rule, our most severe cases; they were more spastic than those with other allergies, and their tremors were much more difficult to

control. Sixty-one of our patients reacted strongly to scratch testing with food allergens. However, we did not depend upon the scratch test wholly, and in the severe cases we used elimination diets and careful observation of the effects of various foods from a clinical standpoint. In Case No. 3, eggs would produce nystagmus immediately. Cases No. 22 and No. 55 would have aggravation of symptoms following the drinking of tea, and Case No. 20 would suffer an aggravation of symptoms immediately following the eating of pork. Case No. 47 became worse symptomatically, and, in studying her diet, we found that she had been eating a large quantity of rhubarb, which was seasonal. The patient had not been tested for her allergic sensitivity to rhubarb, therefore we eliminated it from her diet at once and her symptoms began to improve. At the end of two weeks, her condition had returned to what it was symptomatically prior to the eating of the rhubarb.

Twenty-six had allergic rhinitis. Twenty-two were sensitive to various molds. Twenty-four had eczema or had suffered from eczema previously. Seventeen were sensitive to epidermals. Twelve were sensitive to pollens. Eighteen gave a history of hay fever. Sixteen gave histories of asthma, and ten gave histories of urticaria. Two of our patients with multiple sclerosis grew worse while being treated. Of these, Case No. 33 suffered from a vicious exfoliative dermatitis which came on at the same time the multiple sclerosis symptoms first developed; she was very sensitive to house dust and cotton. Histamine appeared to be of very little value in her case, either for the dermatitis or the multiple sclerosis. The second case which grew worse was Case No. 98. This patient had many blebs on his body at the time his symptoms of multiple sclerosis grew worse, and neither were improved by histamine. Both of these patients suffered from hematuria with a mixed infection pyelitis. Case No. 1 was sensitive to many molds; he had been a yeast maker during the onset of his multiple sclerosis. Case No. 10, a barber, whose wife now operates a beauty college, reacted to human hair. Case No. 46, who had formerly been a printer, reacted violently when tested for newsprint sensitivity. No. 52 was very sensitive to lacquers; before the onset of his multiple sclerosis he had been an automobile painter, using a spray gun. Pregnancy apparently may play an important part, as twenty-four of the sixty-two married women treated by us developed the symptoms of multiple sclerosis during pregnancy or shortly thereafter. Four of these patients had cesarean section. Of the forty-eight male patients, eleven gave histories of major trauma immediately or shortly before their symptoms of multiple sclerosis first appeared; and ten of the forty-eight men developed their first symptoms of multiple sclerosis while serving in the armed forces during World War II.

Tabulating the results of our treatments up to date, we find the following:

## MULTIPLE SCLEROSIS—JONEZ

Objectively symptom free.....	13
Marked improvement objectively.....	20
Improved objectively .....	38
Slightly improved objectively.....	33
Improved subjectively .....	8
No improvement subjectively or objectively.....	10
Worse than at the beginning of treatment.....	2
Total .....	124

Included in the above are the six acute cases, of which four are now objectively symptom-free, one markedly improved objectively, and one worse.

In some of the cases there was no improvement noted until about three months' time had elapsed, this improvement becoming more marked usually after about six months' treatment. However, in a great many of the milder cases, improvement began after a shorter duration of treatment. We are of the opinion that regardless of how soon improvement is noted, intravenous histamine should be continued regularly for at least one year, and much longer in most of the chronic progressive type of cases.

### CONCLUSIONS

The study of our 124 patients has resulted in the following conclusions:

1. Multiple sclerosis is much more prevalent than commonly supposed.
2. Allergy management is apparently indicated in multiple sclerosis to get the maximum degree of improvement.

3. Early treatment yields better results and a greater possibility of bringing about a remission.

4. Histamine diphosphate given intravenously and subcutaneously is of great value, but must be given regularly and over a long period of time.

5. d-Tubocurarine, in oil and wax, controls spasticity or brings about improvement where tremors and urinary incontinence exist. Improvement or control took place quickly in over 80 per cent of our cases.

6. Muscle re-education with physical therapy increases the value of d-Tubocurarine.

7. Because of the time necessary for treatment and the expense involved, available financial aid is needed in any attempt to solve the problem of multiple sclerosis. Local organizations with affiliations, such as the National Infantile Paralysis Foundation, should be set up. Due to the crippling nature of the disease, the average patient cannot carry on financially for the time necessary as a private patient. Education and information, regarding the fact that the sufferers of this disease are not entirely hopeless, should immediately lead to a movement in the direction of adequate care and study of this crippling disease.

8. We do not claim to have cured a single case, although remissions have occurred following treatment, and a large majority of our cases have improved objectively. Practically all of our patients feel they have something to look forward to in the way of treatment, with hopes

for the future. This helps their morale and they are at least subjectively better. If, by treatment, we can make ambulatory or wheel-chair cases out of the bedfast ones, get some from their wheel-chairs onto canes and get others to discard their canes, much will have been accomplished.

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(Continued on Page 578)

# A CHEMICAL CONCEPT OF IMMUNITY

WERNER J. SUER

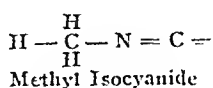
Cincinnati, Ohio

IMMUNITY continues to be so much a play with mere words that any attempt at chemical explanation should be welcomed. Few such have been made. Arrhenius and Madsen<sup>1</sup> showed that the union between a toxin and its antitoxin (diphtheria, tetanus) was like the neutralization of a weak acid by a weak alkali; and Bordet<sup>2</sup> declared it to be like a union between a dye and a fiber, at the latter's surface. Linus Pauling<sup>3</sup> has proposed that what is the (unknown) chemical termed a toxin is rendered inert through intramolecular rearrangement.

My own consideration began in the attempt to give chemical definition to what E. C. Rosenow had discovered as the toxic *antigen* of various streptococci and the *antibody* prepared therefrom. The latter was accomplished by subjecting streptococci and streptococcal antigen in sodium chloride solution, in an autoclave, to prolonged heating. Addition of hydrogen peroxide shortened the time required. Rosenow found the antigen and toxic factors in streptococcal suspensions to decrease and substances resembling antibody to increase under such treatment. The assumption is that the processing converts the antigen into antibody<sup>6,7</sup>.

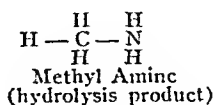
An immunological reaction consists in a newly formed antibody combining with its antigen to yield the immune body. This not only detoxifies the antigen but leads to the formation of further substance able to react with the antigen. The overplus represents the immunological reserve.

A type of organic reaction which suits this pattern is represented by what happens to an isocyanide (also called an isonitrile) when, through hydrolysis or reduction, it is converted to an amine. The former represents the toxin or antigen; the latter, the antitoxin or antibody. Simple illustration of the construction of such chemical bodies appears in the following formulas:



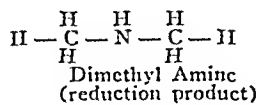
Methyl Isocyanide

ANTIGEN



Methyl Amine  
(hydrolysis product)

ANTIBODY



Dimethyl Amine  
(reduction product)

ANTIBODY

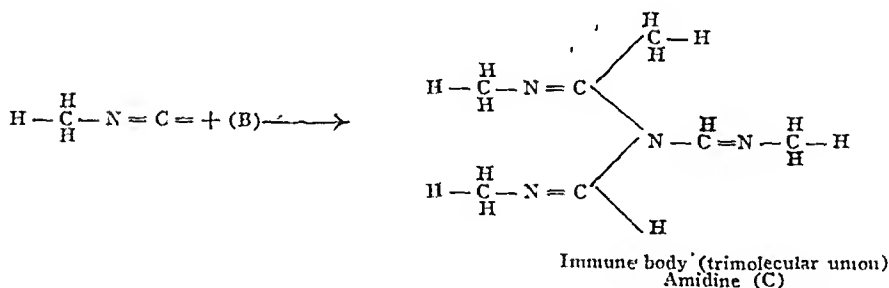
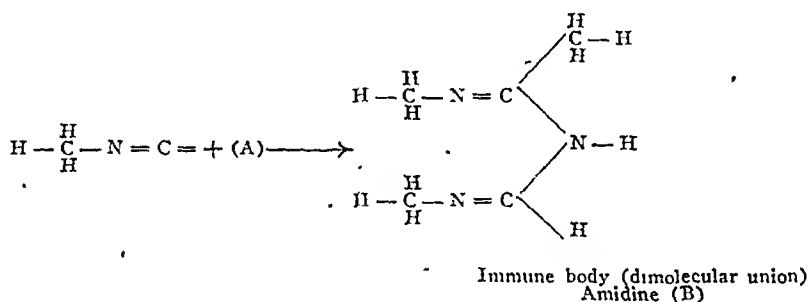
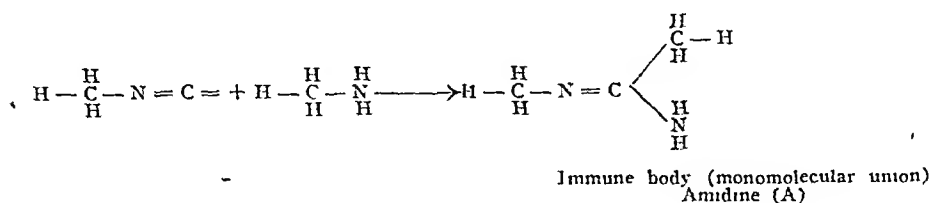
The immunological reaction consists of the union of antigen with antibody to form an amidine. In the illustration used, this transformation takes place in three steps as shown on the opposite page.

As indicated, one molecule of antibody is thus capable of neutralizing three molecules of antigen.\* Since immune body production would not, in

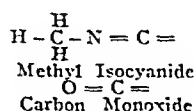
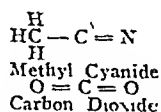
From the Eichberg Laboratory of Physiology of the University of Cincinnati.

\*The structural formulas of the amidines are often written in isomeric forms to those given above. They possess considerable bacteriostatic power.<sup>3,4,5</sup>

chemical terms, proceed beyond the first step in a disease attack, it follows that the intoxicated individual would have left over a reserve of immunity, potent in overcoming the arrival of more toxin. This explains why, because of immediate and large antibody production, the highly intoxicated organism inclines to recover more suddenly than one less poisoned, even though the continuing state of intoxication warrants the anticipation of his getting worse. Thus, the more seriously ill person is better off, in a certain sense, than one less stricken; his antibody production is greater.

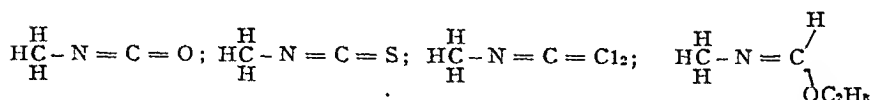


The isocyanides should not be confused with their relatively harmless isomers, the cyanides. (The two forms exist in many cases in equilibrium with each other). Methyl cyanide, for example, is a relatively harmless substance, but not methyl isocyanide. The latter compound (here suggested as the chemical equivalent of antigen) may be compared to carbon monoxide; the former to carbon dioxide.



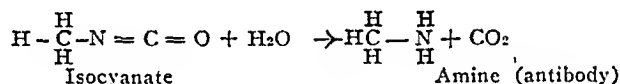
The isocyanide and carbon monoxide both carry a terminal pair of free bonds and similarly are toxic.

The unsaturated bonds of the isocyanide, in addition to combining with ammonia and amines, can also combine with oxygen, sulphur, chlorine and alcohol. The various derivatives would be represented by:



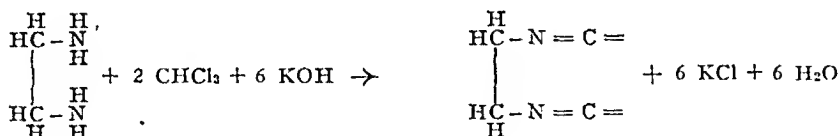
The therapeutic administration of oxygen and of sulphur in various forms has long been considered to have value in chronic infections; and alcohol has been used with good effects in acutely stricken persons. As here seen, alcohol has a direct combining value with isocyanide besides therapeutically making for vasodilatation and thus increased oxygen supply. All these substances have at least a transient power of neutralizing isocyanides (here put in parallel with toxins). They have nothing to do however with the mechanism of producing antibody.

In E. C. Rosenow's conversion of antigen to antibody, hydrogen peroxide leads to quickest effect. The oxygen converts the isocyanide to isocyanate, which then accelerates the production of amine.



#### EXPERIMENTAL

(1) *Preparation of an Isocyanide as Antigen.*—An isocyanide produced from ethylene diamine by the carbylamine reaction (known as the test for primary amines) yielded the garlic-odored isocyanide, ethylene diisocyanide.



In pharmacological tests, Rosenow found that 1/100 gm. of this impure product killed mice on intravenous injection, in one minute, through respiratory failure; 3/1000 gm. elicited violent respiratory movements followed by slight general spasms and a rapid and shallow type of respiration; 1/1000 gm. yielded these symptoms in milder degree, associated with much scratching of the head.

(2) *Preparation of an Amine as Antibody.*—A mixture of 1 c.c. of ethylene diisocyanide with 100 c.c. of water and 1.4 c.c. of concentrated HCl was refluxed in a flask for three hours. All odor of the isocyanide disappeared. The mixture was neutralized with NaOH solution, the hydro-

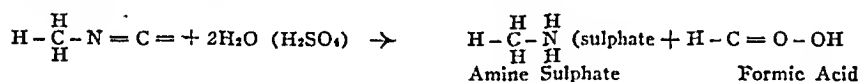
lytic product being an amine hydrochloride in physiologically normal salt solution.

(3) *Preparation of an Amidine as an Immune Body*.—The addition of  $\frac{1}{2}$  c.c. of ethylene diisocyanide (1) to 50 c.c. of the amine solution (2), shaken intermittently for twenty-four hours, made all odor of the isocyanide disappear. While the product of (1) killed mice within one minute, that of (2) antibody and (3) immune body proved harmless.

(4) *Attempt at Chemical Analysis of Streptococcal Antigen and its Antibody*.—A strip of moistened litmus paper, exposed to the distillation vapors when Rosenow's streptococcal suspension is evaporated to dryness on a steam bath, shows no color change upon the addition of 10 per cent NaOH solution. When the antibody is so treated, the indicator turns blue. In the latter case a volatile gas, ammoniacal or amine in type, has been formed and volatilized. This is what would happen if the toxin were an isocyanide and the antibody an amine.

I found that particles of zinc added to the alkalinized steam-bath-dried streptococcal suspension, in this experiment, brought about a hydrogenation, as evidenced by the giving off of an alkaline gas. This means that the toxin yields an amine upon reduction, further proof that an isocyanide was present in the original suspension.

If dilute sulphuric acid is used instead of NaOH solution, an acid gas is volatilized from the dried streptococcal suspension but not from the antibody. An isocyanide present (let it again be held in mind as antigen) should break up as follows, and this it does:



The expected identification of the volatile acid is formic acid. I found the gas to be pungent and capable of decolorizing acidified potassium permanganate solution. The material involved is obviously a strong reducing agent. Formic acid is one of the best of these.

When Rosenow electrolyzed his antibody solutions, he noted an immediate release of an alkaline gas at the negative pole; his streptococcal suspensions (antigen), however, yielded such only much later. In the latter instance, the presumed chemical must first be formed through reduction by the liberated hydrogen before the alkaline gas can come into being. The chemical sequence is identical with that just described.

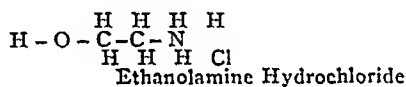
(5) *Isolation of the Streptococcal Antibody*.—This was attempted over two routes. As an amine, antibody should be sublimable as the hydrochloride from a steam-bath-dried sample. This was accomplished by covering the dried residue on a watch glass with a beaker, and heating on an electric plate. The sublimate consisted of crystals which had a build typical



of ammonium or amine hydrochloride. Rosenow tested solutions of these crystals to find that they agglutinated the streptococci as does the antibody itself.

Still better results were obtained toward isolation of the antibody by making the antibody solution slightly alkaline and by steam-distilling it. The distillate was caught in N/100 HCl and evaporated to dryness as the hydrochloride. It had the typical amine hydrochloride structure, identical with those obtained from the hydrolyzed or reduced product of the isocyanides. This product, too, had a high streptococcal agglutination power (1:2500 as 2 plus; 1:3100 as 2 plus; neither being toxic to mice—Rosenow).

(6) *Various Simple Amines Tested for Antibody Effects.*—N/200 solutions of the hydrochlorides of the following amines, in physiological salt solution, were submitted to Rosenow for testing: ammonia, methyl amine, di-*n*-propylamine, di-*n*-butylamine, tri-*n*-butylamine, ethanolamine and triethanolamine. Of these the hydrochloride of ammonia had no effect, but those of methylamine, di-*n*-butylamine, tri-*n*-butylamine and ethanolamine, in this order, showed increasing agglutinating power on several types of streptococci. Least toxic upon injection into mice, and of greatest agglutination power, were methylamine and ethanolamine hydrochlorides.



## SUMMARY

Isocyanide structure is offered as the chemical characteristic of toxin; an amine derived therefrom, as antitoxin; the amidines resulting from combination of the two, as immune body. The organic cyanides were likened to carbon dioxide, as the isocyanides were likened to carbon monoxide. Attention was called to several addition reactions of the isocyanides other than those of the amines. An isocyanide as antigen, its derived amine as antibody, and the amidine as immune body, were made in the laboratory and tested for toxicity on mice. The outcome confirmed the expected. Chemical tests made upon E. C. Rosenow's streptococcal antigen and antibody gave evidence that the former contains isocyanide and the latter, amine. A substance with properties typical of an amine hydrochloride, and highly agglutinative, was crystallized from Rosenow's antibody. A short series of simple amine hydrochlorides was tested for antibody properties. Of the group, methylamine and ethanolamine hydrochlorides were found to be the least toxic and to exhibit the highest agglutinative power.

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(Continued on Page 599)

## CLINICAL OBSERVATIONS WITH THEPHORIN—A NEW ANTIHISTAMINIC DRUG

LOUIS STERNBERG, M.D., and JAMES GOTTESMAN, M.D.

New York, New York

WHEN Dale and Laidlaw, in 1910, pointed out the close resemblance between the effects of histamine injected intravenously into guinea pigs and the symptoms of anaphylactic shock, they laid the cornerstone for the histamine concept of allergy. Subsequently, a chain of experimental evidence was furnished by other investigators indicating that histamine or a histamine-like substance is the probable mediator of anaphylactic symptoms. However, attempts to build up an active immunity to histamine by giving gradually increasing doses of this amine to allergic patients have failed. Histamine-azoprotein also proved ineffective therapeutically. Similarly, histaminase, which destroys histamine *in vitro*, was disappointing clinically. Chemists have sought, therefore, for other substances which are capable of neutralizing the effects of histamine. Fournneau, Bovet, Halpern, and other French scientists found that certain phenolic ethers are potent histamine antagonists, but their early compounds proved too toxic for clinical use. Later it was demonstrated that Antergan and Neo-Antergan, both derivatives of ethylenediamine, are very effective in protecting experimental animals against histamine-induced bronchospasm and that they are less toxic than the original phenolic ethers. Both these preparations have been widely used in France since 1942 in the treatment of allergic disorders. In this country, Loew and his collaborators introduced another phenolic ether, Benadryl, and Mayer and associates produced another ethylenediamine, Pyribenzamine, and both these preparations established themselves promptly in therapeutics. However, many patients taking these drugs develop unpleasant side reactions, among which drowsiness and depression are most commonly encountered.

Therefore, pharmaceutical companies have continued to search for safe and effective antihistaminic drugs. Among the new arrivals, Thephorin\* seemed of particular interest inasmuch as its chemical structure is radically different from that of the histamine antagonists previously reported. This compound, which was prepared by Wenner and Plati,<sup>5</sup> is chemically 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate. The pharmacology of the stable, water-soluble, white powder has been adequately described by Lehmann. According to him,<sup>3</sup> Thephorin antagonizes important physiological actions of histamine in experimental animals; e.g., it prevents histamine-induced contractions of the smooth muscle of the bronchi and intestine; furthermore, it abolishes the effect of histamine on blood pressure and capillary permeability and it is of value in preventing

\*From the Department of Allergy, Beth Israel Hospital, New York, New York.  
\*\*"Roche" brand of phenindamine. We are indebted to Dr. Leo Pirk of Hoffmann-La Roche, Inc., Nutley, New Jersey, for generous supplies of Thephorin.

anaphylactic shock. Acute toxicity studies, likewise according to Lehmann,<sup>2</sup> showed that in mice the LD<sub>50</sub>\*\* of Thephorin was about the same as that of Benadryl, but, by the intravenous route, the new compound proved only one-half to one-third as toxic as Pyribenzamine. There was no indication of chronic toxicity of Thephorin in either rats or dogs.

With this evidence of antihistaminic activity and of comparatively low toxicity, we embarked upon clinical trials.

The case material consisted of seventy-six adult patients complaining of symptoms which were either proved or thought to be of an allergic nature. The types of cases included nasal allergies, both of the seasonal and non-seasonal variety; bronchial asthma, urticaria, and migraine. However, only patients with a diagnosis of hay fever and asthma were represented by sizable numbers. All subjects had been given hyposensitization treatment but were not adequately relieved. Thephorin was administered in 25 mg. tablets. These were prescribed on a three-times-daily basis. In some instances, the daily dose was increased to 100 mg. As relief was obtained, the dose was generally reduced with the object of establishing a maintenance dose.

Side effects occurred in five patients. They all complained of insomnia and one of them also of nausea. These reactions were not severe and abated promptly on discontinuation of the drug. None of the subjects studied experienced drowsiness or depression. Two patients received a daily dose of 75 mg. of Thephorin for three months. Physical examinations, urinalyses, hemograms, and electrocardiograms done for these subjects before, during and at the end of the three-month period failed to reveal any evidence of toxic effects.

TABLE I. RESULTS FROM THEPHORIN THERAPY  
IN 76 ALLERGIC PATIENTS

Diagnosis	Cases	RESULTS		
		Good	Fair	Negative
Hay Fever .....	41	18	4	19
Bronchial Asthma .....	26	9	4	13
Vasomotor rhinitis .....	6	0	3	3
Urticaria .....	2	2	0	0
Migraine .....	1	0	0	1
Totals .....	76	29	11	36

The results obtained are listed in Table I. It appears that of the forty-one patients with hay fever, twenty-two were benefited, with eighteen deriving good relief and four fair relief, and nineteen were not improved. Furthermore, it can be seen from the table that of the twenty-six patients suffering from asthma, thirteen were relieved and thirteen were not benefited. It is interesting to note that the asthma cases which were improved were inhalant patients whose sinuses did not reveal any pathologic basis. On the other hand, seven of the thirteen asthmatics deriving no benefit showed nasal pathologic conditions. Of the six subjects with a diagnosis of

\*\*LD<sub>50</sub> is defined as the dose which is lethal for 50 per cent of the animals used in the experiment.

## THEPHORIN—STERNBERG AND GOTTESMAN

nonseasonal vasomotor rhinitis, three derived some degree of benefit and three were not improved. The two cases of urticaria obtained good relief, but the patient suffering from migraine was not benefited.

### COMMENTS

While the series presented is small, the results obtained indicate that Thephorin is an effective histamine antagonist. Since side reactions are negligible, Thephorin can be used with impunity in patients who do not tolerate Benadryl and/or Pyribenzamine. In fact, it may be advantageous to try Thephorin initially, thus sparing many a patient the trouble of experiencing the unpleasant reactions which are so commonly encountered with the antihistaminics of the older type.

Reynolds and Horton<sup>4</sup> have recently presented their findings with Thephorin. They reported sixty-two patients, of whom thirty-nine were benefited. Of the seventy-six patients we studied, forty derived benefit. Thus, our results are somewhat less favorable than those of Reynolds and Horton. This may be due to the fact that they used somewhat higher doses of Thephorin. However, we are in complete agreement with these authors that Thephorin is distinguished by low toxicity. Similarly, Criepp<sup>1</sup> states that, "Unlike the other drugs, it" (sc. Thephorin) "does not produce drowsiness and sleepiness."

It must not be forgotten, though, that all antihistaminic drugs are only palliatives. None of these preparations will relieve the physician from attempts to recognize the offending allergen and to eliminate it or to hypersensitize the patient. The antihistaminics have a place in conjunction with the orthodox therapy when the latter does not adequately control the symptoms or before it brings relief to the patient.

### SUMMARY AND CONCLUSIONS

Seventy-six patients complaining of various allergic manifestations were treated with Thephorin, a new antihistaminic drug, which belongs to a heretofore unknown class of compounds.

The results obtained are presented in tabulated form. The almost negligible side effects appear to be an attractive part of the new compound. In particular, it is not conducive to drowsiness. It is concluded that Thephorin is a useful drug in the symptomatic treatment of allergic conditions.

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## ADEQUATE DIETS IN ADVANCED CHRONIC ASTHMA

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**M**ALNUTRITION among patients with advanced asthma is common. Rackemann<sup>1</sup> employed the term "depletion" in elaborating on this clinical feature of chronic asthma. Without presenting clear evidence of a lack of individual metabolic constituents, he believes that there must be serious deficiencies in these patients because of their malnourished and debilitated appearance. There is no proof at this time that such deficiencies exist, except that during an acute attack of asthma considerable loss of water takes place (Stoesser,<sup>4</sup> Sheldon<sup>3</sup>). When this occurs frequently, it might perhaps contribute to some loss of weight.

More significant, however, is the fact that many patients are following inadequate diets. The fear of experiencing an ill effect from eating certain foods often induces the patient to avoid these foods for months or even years, contrary to medical advice.

It is generally accepted that diets are essential in the treatment of asthma. The majority of allergists employ temporary, others more or less permanent, elimination regimes which are usually based on skin tests. Others use such standard elimination diets as the ones advocated by Rowe.<sup>2</sup> Others eliminate empirically certain foods which are thought to be frequent sources of asthmatic attacks, such as milk, wheat or eggs. This is subsequently followed by gradual addition of the eliminated articles.

Only a few disregard food sensitivity altogether and advise their chronic patients to eat whatever they desire. In order to investigate this latter, rather unconventional procedure, a series of patients with advanced chronic asthma who were markedly undernourished were placed on an adequate and high caloric diet, disregarding entirely their sensitivities to foods as determined both by clinical observation and by skin tests.

We were concerned with two questions: (1) In what proportion of cases would the asthma become either aggravated or ameliorated? (2) How would this diet affect the patient's nutritional state?

### METHOD

Fifty-six\* patients were selected for this study on the basis of their being below their optimal weight and of having chronic asthma which was proven to be of allergic origin and uncomplicated by such secondary changes as bronchiectasis or pneumonitis. All patients exhibited positive skin reactions to foods as well as to other substances. The duration of their disease ranged from one to twenty years. Six patients had had no previous

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\*Including seventeen children below fifteen years of age.

treatment in our office, while fifty had been under observation and treatment for several months or years. At the time when this study was started, their disease had shown no tendency toward improvement. While the observations concerning the diet were carried out, no change was made in the patient's routine. The new patients received no treatment other than the diet, but were instructed to abide by the routine which they had followed before they came under our care. The diets ranged from 2,000 calories to 4,000 calories, the average being 2,600 calories. The adequacy of the caloric intake was judged by the patients' weight; an effort was made to have them attain the "ideal" weight for their age and height.<sup>†</sup> Emphasis was placed on inclusion of all foods which had formerly been eliminated.

It has been our experience that any ill effect derived from food to which sensitivity exists, becomes manifest within several hours after its ingestion. Conversely, any mode of treatment, if effective in chronic asthma, should accomplish results within a day or two after its initiation. A period of close observation of two weeks, therefore, was considered appropriate for our purpose. During this interval the patients were seen every second day; they were then followed up weekly or bi-weekly for at least three months.<sup>\*\*</sup>

Careful records were kept on three points: (1) the number and severity of attacks before and after the diet was instituted, (2) the gain or loss of weight while following the diet, (3) the patient's own impression of the effect of the diet on his general health.

Before discussing our results, it is of interest to review briefly some of the data obtained from the history taken by the dietitian (MMH) for the purpose of evaluating the patients' diet prior to the two weeks' period of observation. Of the fifty-six patients, only thirteen had not been restricting their food intake; forty-three (including fourteen children) had been adhering to some form of elimination procedure, ranging from avoidance of a few individual items which they themselves considered harmful, to strict elimination diets prescribed either by ourselves or by other physicians. While these diets had been planned to be of sufficient caloric value and to be adequate in vitamins and other food essentials, they actually were lacking considerably in this respect. In thirty-eight of the forty-three patients there was a history of sensitivity to certain foods, yet in twenty-nine, the elimination procedures had not contributed perceptibly to the control of asthma; four were under the impression that food elimination had aggravated their disease. However, six of the forty-three patients had noted a general improvement of their asthmatic state, and four had been temporarily better on food elimination. In some of these individuals, considerable persuasion was required to induce them to follow the new dietary regime.

The average weight below the optimum for their height and age in the

<sup>†</sup>The food groups listed in the "basic seven" recommended by the National Research Council served as a guide to evaluate the patients' food intake.

<sup>\*\*</sup>Extending from mid-July through October, 1946, a period which coincides with the late grass and ragweed season.

fifty-six patients was 8.1 kg. The dietitian's history indicated that there had been a very conspicuous lack in daily caloric intake in thirty-eight patients and a striking deficiency in protein intake in the diet of thirty-one. Two of these individuals presented edema about the ankles and eyes, which was believed to be due to nitrogen deficiency. In sixteen patients, vitamin deficiencies were suspected because of such manifestations as dryness of the skin, bleeding gums, dryness of the tongue and lips, and paresthesias in the extremities.

### RESULTS

Fifty patients were able to tolerate the diets without ill effect. Three of the remaining six suffered severe attacks of asthma when they attempted to eat the added foods which had previously been eliminated; they were obliged to give up further efforts to follow our regime. The other three succeeded in following the diet in spite of several unsuccessful attempts. While following the diet for two weeks they developed such symptoms as rhinorrhea, nasal blockage, minor asthmatic seizures, headache and general weakness. In one patient, marked flatulence and gastric discomfort occurred.

The average gain in weight in forty patients was 1.52 kg. during the two weeks' period. In ten there was no change, and in the three who developed untoward symptoms, there was an average loss of .75 kg. One patient (Mr. A. S.) gained 3.4 kg. on a diet of 4,000 calories. In conjunction with the gain of weight, they noted a general subjective improvement, a return of their physical strength and a great change in their mental outlook.

As to the effect of the diet on the asthmatic attacks, there was an aggravation in the three individuals as noted above; no change was detectable in ten, while in forty the number and severity of the seizures lessened appreciably. Of this latter number, twelve patients remained free from attacks for more than three months. The improvement in the patients' nutrition paralleled strikingly that of the asthma.

The following two case reports present typical examples illustrating the manner in which the patients responded to the diet.

### CASE REPORT

*Case 1.*—Mrs. L. C. L., aged thirty-seven, had been under our care since March, 1938, having been afflicted then with bronchial asthma for one year. At first, the attacks were present perennially, with some aggravation during and following each ragweed season. They ceased completely from June, 1943, until February, 1945. Since then she suffered daily attacks except for brief periods while she was hospitalized. During the past three months the seizures had become so severe that they did not yield to the usual symptomatic treatment (aminophylline, ephedrine, epinephrine). The patient had experienced sensitivity to various foods, especially to certain meats, fish and eggs, which she had been avoiding. She also had noted sensitivity to house dust. Intradermal skin tests in 1938, in 1945 and in 1946

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revealed major reactions to these substances as well as to ragweed, grass pollen, and several fungi. There were other reactions to numerous foods and inhalants.

The physical examination revealed an underdeveloped and emaciated white female with considerable dyspnea, her weight being 47 kg., the estimated weight for her age and height being 57.5 kg. There was no evidence of infection in the nose and sinuses; the nasal membranes exhibited a typical allergic appearance with considerable edema and pale, bluish discoloration. The chest findings were characteristic of advanced asthma with marked emphysema and a tendency to pigeon chest. X-ray and blood studies were negative except for a blood eosinophilia of 12 per cent.

The patient had been receiving injections of pollen, fungi and other inhalants to which she was sensitive. She had been on elimination diets of Rowe, and on other occasions on strict avoidance of the large variety of foods to which she had reacted on skin testing in 1938 and 1945. Her daily caloric intake was estimated at between 1,400 and 1,900 calories.

On July 27, she was asked to disregard all former food sensitivities and follow a full diet of 2,600 calories. Within twenty-four hours she reported that she was able to sleep through the night for the first time in months. At the end of the first week she had gained 1.1 kg. Her asthma had ceased entirely during the day, and minor attacks, occurring only at nighttime, were readily controlled with  $\frac{3}{8}$  grain of ephedrine sulfate and  $1\frac{1}{2}$  grains of aminophylline. The hyposensitizing injections were carried on at weekly intervals throughout the ragweed season. The patient was entirely free from asthma until December 24, 1946, when she developed slight wheezing following an upper respiratory infection. This cleared up spontaneously within two days. On January 24, 1947, she had still been free from wheezing; her weight was 56 kg. and she had been in the best of health.

*Case 2.*—Miss M. W., aged twenty-nine, had been under our observation for seven years. She had been one of the most intractable cases encountered in our practice. The asthma began in 1939 at the height of the timothy season. At first, there had been brief periods of freedom from attacks; since February, 1943, however, the attacks had been present more or less continuously. Practically every night she had to resort to inhalation of epinephrine and occasionally to hypodermic injections ranging from 0.1 c.c. to 0.2 c.c. Repeated physical examinations, several rhinological, bronchoscopic and x-ray examinations revealed entirely negative findings except for the presence of emphysema and the physical signs in the lungs of uncomplicated bronchial asthma.

According to her history, milk, all fowl, most nuts and beans disagreed with her. She had attempted to avoid these foods for years, paying particular attention to such avoidance when there was an aggravation of her attacks. However, the intradermal skin tests done in 1943 were entirely negative. When repeated in September, 1945, and again in June, 1946, they showed strongly positive reactions to a large variety of antigens of all types. These reactions varied greatly upon each testing. The elimination diet based on these tests, as well as injections of pollen, fungi and house dust failed to produce results. On one occasion intramuscular injections of milk (0.2 to 1.0 c.c. daily) brought about complete relief from asthma for five days, but were ineffective on subsequent trials. Milk had been the only food which had given constantly strong positive reactions on repeated testings.

On August 7, 1946, when her weight was 51.5 kg., the patient was given a diet of 2,600 calories, disregarding all food sensitivities. Within forty-eight hours she reported marked relief from asthma; within a week she became entirely free from attacks, and had gained 1.9 kg. Subjectively, she felt better than at any time during the past three years. This improvement lasted for six weeks, during which the hyposensitizing injections were carried on in the same manner as before. Then,



slight attacks began to recur every second to third night, which were readily controllable by  $1\frac{1}{2}$  grains of aminophylline orally. In mid-November, this condition became aggravated by what appeared to be an upper respiratory infection with fever up to  $101^{\circ}$ . The attacks have appeared more frequently since, but have been much less severe than at any time since the patient came under our observation. Her weight on February 1, 1947, was 62.2 kg.

#### COMMENT

These two cases were selected here because they constitute typical instances of the forty patients who benefited from the diet, from the point of view of severity and chronicity of the disease. They also illustrate how the benefits from the diet were maintained; twelve patients have actually become entirely free from asthma as in Case 1, while others have experienced a relapse into the asthmatic state. But even in the latter group, marked general improvement persisted for a long time. Because of the well-known difficulties encountered in maintaining a critical judgment in interpreting results in chronic asthma, no further elaboration on the degree and permanency of the improvement is made here. Case 2 furthermore illustrates a common observation concerning food sensitivity, namely, that reactions to foods, in contradistinction to those to pollen and other inhalants, do not tend to remain constant on repeated testing. Similarly, foods which account for asthmatic attacks on one occasion may be eaten with impunity at other times.

#### DISCUSSION

While no attempt is made here to present statistical data, certain reasons lead one to expect that advanced chronic asthma is frequently accompanied by malnutrition. Asthmatic attacks often interfere with the process of eating through the embarrassment in breathing. Sometimes the slight exertion required for eating seems to aggravate attacks, thus deterring the patient from eating properly. Furthermore, the drugs usually employed for asthma (as ephedrine, the new antihistamine drugs, and aminophylline) may induce gastrointestinal disturbances and thus interfere with appetite and digestion. The chief reasons, however, for the patients' malnutrition, judging from our observations and from discussions with the individual patients, is their anticipation of developing asthma if they eat certain foods. This fear is based largely on their own unpleasant experience of having suffered attacks from foods to which they had been sensitive at one time. Sometimes the physician who places too much emphasis upon food sensitivity enhances the patient's concern about foods. A great deal of persuasion is often necessary to have them follow a more adequate dietary regime once they are in the possession of an elimination list.

Only six patients could not tolerate a diet containing the foods to which they had been clinically sensitive or which had given positive skin reactions. This indicates that food does not play a major part in the majority of the patients with asthma, an observation which is in striking

contrast with the views of many allergists. Yet, it also suggests that in a few instances, approximately 10 per cent, food cannot be disregarded as a major cause of the attacks. In young children and infants, who were not represented in our group, food undoubtedly is of greater importance than in adult asthmatics.

In view of this discrepancy of opinion concerning the role played by food in chronic asthma, one wonders to what extent psychogenic factors enter into this subject. In watching these patients closely, we were indeed reminded of the startling "cures" of asthma effected by certain charlatans. One of us (G.L.W.) has had occasion to analyze the detailed "case records" of such "cures." Most of the patients had been urged by the "doctor" in question to disregard all food sensitization. There are many reasons<sup>6</sup> for an individual afflicted with chronic asthma to develop a psychosomatic aggravation of the disease which may in time become its dominant feature. By the same token, the reverse may hold true, namely that the startling results which are so often encountered from strict elimination diets may in a few instances be effected by the patient's attitude.

This theory, however, is not sufficient to explain our results. In view of the remarkable parallelism in the amelioration of the asthma and the gain in weight, we cannot help but feel that the malnutrition itself and the inherent "depletion" in essential food elements constitutes the major issue in the persistence of the asthmatic state. The addition of these foods may therefore assist in re-establishing the "allergic balance," thus aiding the patient in overcoming the attacks.

#### SUMMARY

1. Fifty-six patients with chronic asthma who were on an average of 8.1 kg. below their estimated weight were placed on diets adequate in calories and in all essential food constituents, disregarding entirely existing food sensitivity.

2. All patients had given positive skin reactions to foods; in thirty-eight the history indicated sensitivity to certain foods. Forty-three had previously been on food elimination regimes with the following results: twenty-nine believed that such diets had had no effect on the course of the asthma; four had noted an aggravation; and ten had experienced temporary improvement of the asthmatic state.

3. The history and examination findings suggested deficiency in protein and vitamin intake in thirty-one patients.

4. Fifty of the fifty-six patients were able to tolerate the diet without ill effect; three developed such severe asthmatic attacks that they had to abandon the diet. Three others were able to follow it during the two weeks' trial period, but suffered some untoward symptoms from the diet.

5. In forty patients the average gain in weight was 1.52 kg.; in ten the weight remained stationary, and in the three who developed untoward

symptoms, there was an average loss of .75 kg. The effect on the asthma paralleled closely the patient's improvement in nutrition. Of the forty patients who were temporarily relieved, twelve remained free from attacks for more than three months.

6. In explaining these results, it is suggested that the deficiency in essential food constituents and in caloric intake ("depletion") contributes to the persistence of the asthmatic state. Psychosomatic factors cannot be excluded.

#### CONCLUSION

It is concluded that patients with chronic asthma who are undernourished may derive great benefits, with respect to their asthma and their general health, from diets adequate in all essentials and of sufficient calories to maintain a normal weight, regardless of the fact that these diets contain foods to which positive skin reactions are obtained and to which the patients had previously reacted clinically. Such diets, however, should be planned judiciously, since approximately 10 per cent of these individuals may experience some ill effects.

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### MULTIPLE SCLEROSIS—TREATMENT WITH HISTAMINE AND D-TUBOCURARINE

*(Continued from Page 563)*

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sensitivity is an infrequent possibility because petrolatum is such a mild substance. In one of the few reports in the literature of sensitivity to pure petrolatum, Hollender<sup>1</sup> states that it is a very poor sensitizer; and even though it is the most widely used ointment base, he was unable to find previously reported cases of sensitization. His case was one of severe dermatitis of the face due to petrolatum applied to the scalp. He obtained a positive patch test by rubbing the material into the forearm four times a day for several days. It required three or four days to produce a positive reaction, which was characterized by a pin-point pruritic vesicular eruption.

Niles<sup>2</sup> reported a case of dermatitis which he proved was due to liquid petrolatum used in a hair tonic. Prior to these reports, Webber,<sup>5</sup> who had compiled a very comprehensive list of external causes of dermatitis from which petrolatum was excluded, commented on this point, "The literature fails to show reports of dermatitis from pure petrolatum because it is one of the most stable bodies and does not contain phenol, cresol or any saponifying matter." Hollender<sup>1</sup> discussed Webber's statement in his paper, and stated that, "This is unquestionably true, for otherwise cases would have been observed and reported, as petrolatum is one of the most widely used ointment bases."

No additional cases of sensitivity to petrolatum have been reported. Sulzberger<sup>4</sup> lists it as a possible irritant. The view of most allergists and dermatologists is that impure petrolatum products may cause dermatitis, such as found among individuals working with machine oils, but sensitivity to the purified materials, as used in ointment bases, occurs with extreme rarity.

Patch tests on normal skin, even with not too highly purified yellow petrolatum, rarely produce a positive skin reaction. Hollender's case gave a positive reaction only after several days of rubbing the material into the skin four times a day. The rarity of reports of petrolatum sensitivity is no doubt partly due to the difficulty in obtaining positive patch reactions to this substance. For this reason, we have relied on the so-called "usage test" in investigating this problem. Our procedure is to supply the patient with small tins of white and yellow petrolatum, anhydrous lanolin, and benzoinated lard. He is instructed to rub each ointment base into different affected sites, each one for several days at a time, noting any exaggeration of the amount of itching and local irritation produced. A small area the size of a 50-cent piece is sufficient for test purposes. The "usage test" can be carried out in any affected area, but the more sensitive sites are the flexural surfaces of the knees and elbows, and the skin above the suprasternal notch and eyelids. A reaction is considered positive when, following the application of any of these materials, itching and erythema are increased. In some of our cases, itching began at the site of a usage test within fifteen minutes or less. Others did not show any irritation until after the application of the material several times a day for several days. Many patients who claimed that, "Any greasy

substance makes me itch," were found sensitive to petrolatum and not to lanolin and lard, and were able to tolerate the latter substances.

There are undoubtedly a number of patients suffering from dermatitis, who are unable to tolerate any greasy substance on the skin. Many such cases may be found sensitive to one of the ointment bases by means of the usage test. Most patients, whom we have found sensitive to an ointment base in this series, were sensitive to petrolatum. A few were sensitive to both petrolatum and lanolin; several were sensitive to lanolin alone. In none have we found a sensitivity to benzoinated lard. The latter substance, however, is very drying and is far from the ideal substitute for petrolatum. As a substitute for a petrolatum-containing ointment base we have found useful an emollient composed of lanolin and/or benzoinated lard combined with Almay Emulsion Base.

#### REPORT ON CASES

*Case 1.*—Mrs. H., aged twenty-nine, had dermatitis of the upper eyelids and neck of six months' duration. The patch reaction to her nail polish was positive. The dermatitis cleared up partially following the elimination of the nail polish. A number of weeks later there was still itching, redness and scaling of the affected areas.

All previous local treatment and cosmetics had been eliminated except albolene which was used to allay the dryness and the tendency to scaling. The emollient cream containing benzoinated lard and emulsion base was substituted for the albolene. The condition cleared up completely within a few weeks. Subsequent trial with petrolatum, mineral oil and albolene at intervals extending over several years always reproduced itching and redness of the eyelids. It was never possible to obtain a positive patch test by rubbing these substances into other areas of the body.

*Case 2.*—Mrs. P., aged forty-two, had severe dermatitis of the eyelids for nine months. The lids were dry, itchy and scaly. There was considerable blepharitis with occasional acute attacks of conjunctivitis. Previous elimination of all cosmetics, creams and nail polishes for several months were without benefit. During this interval the substitution of several brands of "nonallergic" cosmetics and creams produced no change in her condition. The patient was given only white petrolatum to control the severe dryness and scaling of the lids. She stated that following the application of the petrolatum the lids were soothed for several hours and then began to itch again with great intensity. Qualatum, although containing petrolatum, did not produce itching, the petrolatum in this preparation apparently being highly refined and not containing the substances irritating to the patient. A cream composed of Qualatum and emulsion base was substituted for the petrolatum. Within a few days the condition began to clear up; at the end of two weeks it was completely healed and has remained so for over one year. The patient has continued the use of this cream as a substitute for her cosmetic creams.

*Case 3.*—Mrs. B. H., aged thirty, had suffered from a severe dermatitis of the face, neck and extremities all her life. There was a very strong past and family history of allergy, chiefly asthma and hay fever. Several previous allergic studies and subsequent desensitization resulted in variable and incomplete benefit. When first seen, the dermatitis was very violent and acute. The itching was intense, and the patient at times seemed on the verge of a nervous collapse. Sedatives and the liberal use of antihistaminic agents gave only slight relief. She was applying yellow petrolatum freely as a soothing application. As long as this substance was

applied, the tendency to scaling and dryness was overcome, but the itching continued intensely. All previous local medicaments had been eliminated by her dermatologist.

Complete allergic studies were initiated, followed by an elimination and desensitization program. In the meantime, various local medicaments were combined in the special emollient cream mentioned above to allay the itch. It was found by the usage test that this patient was intensely sensitive to Vaseline and lanolin. She was unable to tolerate some of the newer ointment bases containing petrolatum or mineral oil. The persistence of her condition was undoubtedly due to these substances. Several months of both systemic and local therapy, the latter consisting of mild local applications of petrolatum-free and lanolin-free ointments, resulted in almost complete clearing of this condition for the first time in many years. One year after the initial examination the patient was having only occasional mild flare-ups and was leading a normal social and domestic existence. Patch tests with both lanolin and Vaseline on unaffected sites were negative, despite repeated thorough application. However, usage tests after several days on previously affected areas were still slightly positive.

*Case 4.*—Mr. G., aged sixty-six, was a cobbler who developed a severe, pruritic dermatitis of his fingers and hands extending on the flexural surfaces of the arms to the elbows. The condition had persisted for about three months. During this time he had used various ointments some of which he thought aggravated the itching. During a week out of the city, he cleared partially, but still itched severely at times. He continued the use of several of his ointments during this interval.

Allergic study of his case revealed a very strongly positive patch test to a brown ink used for dyeing the edges of new soles. Usage tests for white petrolatum and for several ointment bases that contained petrolatum were positive. Some of these produced itching within a few minutes after they were applied to affected areas. Patch tests on normal skin with these substances were negative. He was able to tolerate lanolin without difficulty.

The skin condition cleared up completely within a few weeks following the elimination from his shop of the incriminated brown dye. During this time he used lanolin exclusively for local treatment.

*Case 5.*—A. B., aged seven, had had facial eczema during infancy, and chronic atopic eczema of the flexural surfaces of the knees and elbows of three years' duration. Complete skin testing revealed sensitivities to numerous foods and inhalants, elimination of which produced only partial relief. Usage tests showed marked sensitivity to white petrolatum and several petrolatum-containing ointment bases. Patch tests for these items were negative. Petrolatum-free ointments were prescribed for local treatment, continuing the elimination and desensitization regime. The condition cleared up rapidly and completely. Some months later, the repeated application of petrolatum to the previously affected areas did not reproduce itching or irritation.

*Case 6.*—Mrs. G., aged thirty-five, was under treatment for seasonal and perennial hay fever. She developed a severe irritation of both her lips. She did not recall any recent change in her lipstick or cosmetics. Several "nonallergic" lipsticks were tried all of which produced irritation of the lips. The cheilitis required from one to three weeks to clear up after each relapse. Patch tests with a number of the dyes and other ingredients used in these lipsticks were negative. During an interval of freedom, white petrolatum and lanolin were applied in turn to the lips. Each of these usage tests was positive within a few days. Subsequently a lipstick was obtained for this patient containing neither lanolin nor Vaseline.† She was able to use this lipstick without return of the cheilitis.

†Lipstick No. 200, Ar-Ex Cosmetic Company, Inc., Chicago, Illinois.

## DISCUSSION

In addition to the six definite cases of sensitivity reported above, several patients have been encountered during the last few years in whom a less definite allergy to petrolatum was suspected. These cases complained of itching after the application of ointments. Usage tests were questionably positive, and the results were too indefinite to include in this report. However, it may be worth while to note that these individuals seemed to do better, and were more comfortable, on petrolatum-free ointment bases. Several were better able to tolerate the newer ointment bases said to contain more highly purified petrolatum or mineral oil.

Sensitization to petrolatum, mineral oil and related substances used in ointment bases must occur more frequently than generally suspected. Otherwise, one observer would not be likely to see such a disproportionate number of cases. The probable explanation of the rarity of previous reports is the fact that reliance for diagnosis has been placed on the patch tests. It should be emphasized that substances as mild as these rarely react to patch tests even when the material is repeatedly rubbed into the normal skin. The usage test is of the greatest value for such substances. By means of this method, the ability of the patient to tolerate these and other medicaments can be rapidly determined, and the diagnosis of sensitivity to various ointment bases can thus be made when suspected.

## SUMMARY

1. Many ointment bases contain petrolatum or mineral oil.
2. Six cases of definite sensitivity to petrolatum or related substances are reported.
3. Patch tests on normal skin for purified petrolatum are rarely positive.
4. Usage tests are a valuable means of making a diagnosis of petrolatum sensitivity. These may be positive on affected sites and later negative on the same healed sites.
5. In view of the widespread use of ointment bases containing petrolatum and/or mineral oil for the local treatment of the allergic dermatoses, the possibility of sensitization to these items should be kept in mind.

\* \* \*

Since this paper was submitted for publication, we have encountered four additional cases definitely sensitive to petrolatum. These were all negative to patch tests, and positive to the usage tests carried out on the affected sites.

One was a case of cheilitis sensitive only to petrolatum and to none of the other lipstick ingredients. The second was a case of seborrheic eczema in a patient who failed to clear despite adequate local therapy until mineral oil was interdicted for local application. The other two cases were typical chronic atopic eczema in children who had failed to respond to the usual allergic studies and desensitization treatment until petrolatum-free ointment bases were prescribed.

*(Continued on Page 593)*



## A STUDY OF ATOPIC ECZEMA

### I. Further Observations on Allergy to Human Dander II. Cutaneous Reactions to Eczema Scales

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IN previous communications<sup>2-6</sup> on the subject of atopic eczema,\* a report was made of the occurrence of cutaneous reactions to human dander in patients with this disease. These reactions consisted of (1) urticarial reactions to scratch test, obtained in older children and adults; (2) eczematous reactions to patch test on normal skin, obtained in a large percentage of children and a small percentage of adults; (3) eczematous reactions to massage or inunction test, which closely paralleled the patch tests on normal skin, and (4) eczematous reactions to patch test applied on scarified skin, obtained in adults (and also obtainable in children).

The hypothesis that human dander is an important allergenic excitant of the disease was stated to rest upon the following evidence: (1) All persons have contact with human dander from their own scalps or from those of others about them, or both. (2) A large percentage of persons with the disease exhibit cutaneous reactions to human dander, whereas in persons without the disease such reactions occur only rarely. (3) The reactions to patch test on normal skin and on scarified skin and those to massage or inunction are eczematous reactions and reproduce the lesions of the disease. (4) Avoidance of human dander is of value in treatment of the disease. (5) The location of the lesions on the face, neck, flexure surfaces such as the cubital space, the upper arm below the lower margin of the sleeve (in children with short sleeves), the cheeks and chin may *partially* be explained on the basis of such factors as proximity to the scalp, exposure to contact with human dander from the parent's head, neck and shoulders, solution and penetration of dander allergen in areas of flexion, et cetera. (6) Scratching is harmful not only because of mechanical injury to the skin but also because the finger nails, due to their frequent contact with the scalp, inoculate the skin with dander allergen.

#### I. FURTHER OBSERVATIONS ON ALLERGY TO HUMAN DANDER

The weakest link in this chain of evidence is item No. 4, which is concerned with the value of avoidance of dander in treatment of the disease. In the previous report (on this aspect of the problem) evidence was based on the favorable results obtained in three of four cases.<sup>4</sup> Since

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\*In other publications on this subject the author has used the terms:

1. "Atopic eczema" synonymous with "atopic dermatitis."

2. "Eczematous" with "characteristic atopic reaction to patch test."

The reason for this in different publications on the same subject is that various editors require the use of certain terms as a prerequisite of publication.

this is an extremely small series and because atopic eczema is capricious in its manifestations, it was considered desirable and necessary to make further careful clinical observations on a larger series of cases, both children and adults. These observations were made during the colder months of the year, October to May, because in a large proportion of the cases the disease improves or disappears in hot weather. Hence, any methods of treatment, begun in May or June and continued for several months, is likely to be erroneously regarded as effective. With one exception these patients were treated in the home. In the selection of cases for study, prime consideration was given to obtaining those patients who (themselves or their parents) gave promise of co-operating reasonably well.

The plan of study included the usual history, physical examination, routine cutaneous tests (scratch method) with foods and inhalants, and patch tests (on normal and on scarified skin) with human dander. These were followed by a preliminary observation period of variable time, usually several weeks. During this period the only local remedies used were cold cream, zinc oxide ointment and calamine lotion. These were used also during the subsequent period of study. During this period an attempt was made to diminish the patients' contact with human dander and to evaluate the effect of such diminution on the clinical course of the disease.

Avoidance of human dander, because of the ubiquity of the substance and its intimate association with human beings, was necessarily incomplete. However, a study of the reactions to patch and inunction tests suggests that an avoidance, even though incomplete, might be of considerable value in treatment, provided that human dander is a major factor in the pathogenesis of this disease and provided it acts through *surface contact* with the skin. The reason for this opinion is that a relatively great exposure is necessary to produce reactions to patch or inunction tests. These reactions, for example, are not nearly of the degree of magnitude of those produced in contact-type eczema by such substances as mercury, nickel, poison ivy, et cetera.

Diminished contact with human dander was to be accomplished by frequent washing of the scalp with soap and water, wearing long sleeves and high-neck dresses, frequent changing of clothing, frequent changing of pajamas and bed linens, wearing long-sleeve pajamas, having parents avoid contact of the child with their face, neck, hair and shoulders, having parents of eczematous children wash their own scalps frequently, enclosing the hair by wrapping with cloth. One child, Case No. 4, was removed to a hospital to avoid her mother's dander. In another Case, No. 11, the hair of the scalp was cut short to facilitate cleansing.

Observations were made on fourteen patients, eight of whom were less than four years of age, the remaining six being nine to thirty-six years of age. All except three were allergic to human dander. These three latter cases were included in the study as "negative" controls.

CASE REPORTS

(Concerning the term "E.M.Z. eczema scales," see Part II)

*Case 1.*—G.S., a boy, aged two, had eczema of twelve months' duration, on the face, forearms and cubital spaces. The eczema was definitely worse in the winter and better in the summer. His mother had perennial hay fever. Urticarial reactions to scratch tests: ragweed pollen, ++; foods, negative. Eczematous reactions to patch tests: human dander, ++; E.M.Z. eczema scales, ++; ragweed pollen, ++++. In spite of careful avoidance of human dander, as thoroughly as could be accomplished in the home, his eczema continued without much change throughout the winter and spring. During the ragweed season in August and September there was no exacerbation of the eczema.

*Case 2.*—B.S.L., a girl, aged two, had eczema of the face, hands, wrists, forearms, cubital and popliteal spaces of twelve months' duration, present all year but worse in the winter. Her great grandmother had asthma. Urticarial reactions to scratch tests: egg, ++. Eczematous reaction to patch tests: human dander, ++++; E.M.Z. eczema scales, ++++. Avoidance of human dander was followed by a great deal of improvement even during the cold winter months. Some lesions, however, persisted.

*Case 3.*—T.O.T., a boy, aged six months, had eczema of three months' duration on the face, upper and lower extremities and trunk. The family history of atopy was negative. Urticarial reactions to scratch tests: egg, ++++. Eczematous reactions to patch tests: human dander, negative; E.M.Z. eczema scales, negative; his own dander, negative; his mother's wool coat, negative. The eczema continued without much change. He sucked both index fingers. These were eczematous. Other fingers which were not sucked appeared normal. Saliva gave a negative patch test.

*Case 4.*—D.H., a girl, aged nine months, had eczema on her cheeks and upper and lower extremities, of four months' duration. The family history of atopy was negative. Urticarial reactions to scratch tests: egg, ++++. Eczematous reactions to patch tests: human dander, ++++; E.M.Z. eczema scales, negative. Her clinical course was very irregular and capricious. Several periods of great improvement were followed by exacerbations. She was placed in the hospital and, after four days without improvement in her condition, was given soy bean milk, cow's milk being withheld from her diet (skin tests to cow's milk were negative). In two days she was much improved. During the succeeding seven days, however, her eczema became greatly aggravated and was really more severe than at the time of admission. This exacerbation occurred while she was on a soy bean diet without cow's milk and without egg. (Eggs were withheld during the entire period of observation—before, during and after hospitalization). She was then put on a cow's milk formula, remained in the hospital four more days, and left with her eczema in practically the same condition as at the time of admission.

*Case 5.*—L.L.W., a girl, aged three months, had eczema on the face only, especially on her cheeks, of six weeks' duration. The family history of atopy was negative. Urticarial reactions to scratch tests: egg, ++. Eczematous reactions to patch tests: human dander and E.M.Z. eczema scales, both negative. The eczema persisted. Avoidance of human dander, as expected, was of no value in treatment.

*Case 6.*—M.A.D., a girl, aged three, had eczema in the cubital spaces and on her forearms and hands of twelve months' duration. The skin was lichenified as in the

adult type of the disease. Unlike most cases there was no seasonal variation in the lesions. Her mother had hay fever. Egg gave a + urticarial reaction to scratch test. Human dander gave a very slight reaction ( $\pm$ ) to patch test. E.M.Z. eczema scales produced a + + + + eczematous reaction to patch test. Avoidance of human dander, as expected, was of no benefit.

*Case 7.*—P.O., a girl, aged three, had eczema of the cheeks and in cubital spaces of two years' duration, present in cold weather but absent in the summer. Her father had hay fever. Egg gave an urticarial reaction to scratch test (+ + +), and when eaten was followed immediately by generalized urticaria (but not by an exacerbation of eczema). Eczematous reactions to patch tests: human dander, + + +; E.M.Z. eczema scales, +. Avoidance of human dander was followed by disappearance of the lesions on the cheeks and improvement of those in the cubital spaces. Residual eczematous lesions persisted, however, in the cubital spaces until the summer season.

*Case 8.*—M.L.B., a girl, aged two, had eczema on the face of one year's duration, better in summer, worse in winter. Her mother had asthma. There were negative urticarial reactions to foods and inhalants. Human dander gave an eczematous reaction to patch test (+ +). Avoidance of human dander was followed by complete disappearance of the lesions in one month.

*Case 9.*—N.J.M., a girl, aged nine, had had eczema in the cubital spaces and on her arms, forearms and neck since infancy. In the past she had also had lesions on the scalp and in popliteal spaces. The lesions were much less extensive and less severe (sometimes disappearing entirely) in the summer. She also had hay fever and asthma, but there was no definite family history of atopy. Urticarial reactions to scratch test: ragweed pollen, + + + +; house dust, + + +; human dander, + + +. Eczematous reactions to patch test: human dander, (on normal skin)  $\pm$ , (on scarified skin) + + +; ragweed pollen, (on normal and on scarified skin) negative; E.M.Z. eczema scales, (on normal skin) negative, (on scarified skin) +. Human dander rubbed on abdomen resulted in numerous itchy papules which persisted for a week. Avoidance of human dander was followed by remarkable improvement lasting many weeks during the winter season. In the cubital spaces and on the neck, however, definite eczematous lesions remained in spite of the best of care in avoiding dander.

*Case 10.*—D.H., a girl, aged thirteen, had eczema of the face, neck, upper chest and upper back in the area not covered by her dress. Her eczema began at two years of age and lasted to three years of age, recurred at six years of age and lasted to present time. Her father's sister had hay fever. Scratch tests gave urticarial reactions to ragweed and grass pollens and to human dander. Eczematous reactions to patch test on scarified skin: human dander, + + (the test was negative on normal skin); E.M.Z. eczema scales, negative. Human dander was rubbed on the same area on an arm once daily for five days. No lesions appeared. She pursued a very irregular clinical course with little, if any, improvement which could legitimately be attributed to avoidance of dander.

*Case 11.*—E.M.Z., a girl, aged thirteen, had had eczema over almost her entire body since six months of age. In the summer it improved remarkably and often left entirely, but recurred every fall and lasted all winter. One sister and one brother had atopic eczema. Urticarial reactions to scratch test: foods and inhalants, all negative. Eczematous reactions to patch test: human dander, (on normal skin) negative, (on scarified skin) + +; E.M.Z. eczema scales (her own), negative on

TABLE I. RESULTS OF DIMINISHED EXPOSURE TO HUMAN DANDER

No.	Age (Yrs.)	Sex	Duration of Eczema	Location of Lesions	Other Allergy in Patient	Family History of Allergy	Urticarial Reactions to Scratch Tests	Eczematous Reactions to Patch Tests With Human Dander		Clinical Course of Disease
								On Normal Skin	On Scarified Skin	
1	2	M	12 mos.	Face, cubital spaces, forearms	—	+	Ragweed pollen ++	++		No definite improvement.
2	2	F	12 mos.	Face, hands, wrists, rt. forearm, pop. spaces	—	+	Egg ++	+++		Much improvement but some lesions remained
3	1½	M	3 mos.	Face, upper and lower extremities and trunk	—	—	Egg +++	—	±	No improvement
4	3½	F	1 mos.	Face, upper and lower extremities and trunk	—	—	Egg +++	+++		No improvement
5	1½	F	6 wks.	Face only	—	—	Egg ++	—	—	No improvement attributable to dander avoidance either at home or in hospital
6	3	F	12 mos.	Cubital spaces, forearms, hand	—	+	Egg +	±	—	No improvement
7	3	F	2 yrs.	Cheeks, cubital spaces	—	+	Egg +++	+++		No improvement
8	2	F	1 yr.	Face only	—	+	—	++		Definite improvement, residual lesions persisted
9	9	F	8 yrs.	Upper extremities, neck, cubital spaces	+	—	Ragweed pollen +++ House dust +++ Human dander +++	±	++	Cleared entirely in 4 wks.
10	13	F	Age—2 to 3 yrs. 6 to 13 yrs.	Face, neck, chest where not covered by dress	—	+	Ragweed pollen + Bluegrass pollen + Human dander +++	—	+	Improvement but lesions persisted on neck and in cubital spaces
11	13	F	12½ yrs.	Generalized	—	+	Human dander ±	—	+	No definite improvement
12	15	F	11 yrs.	Neck, cubital spaces, fingers	+	+	Ragweed pollen +++ Human dander +++	+	+	No definite improvement
13	22	F	21 yrs.	Face, neck	+	+	Dog dander + Human dander ++	—	+	No improvement in 3 wks.
14	36	F	Many yrs.	Face, neck, right cubital space	+	—	Human dander +++	—	+	Great improvement in cubital space. Little improvement in face

both normal and scarified skin. (This patient's eczema scales—designated "E.M.Z. eczema scales"—were found to be the most potent in their capacity to produce eczematous reactions to patch test. On the patient herself, however, they produced no reaction). Her clinical course was modified very little, if indeed at all, by avoidance of human dander. In this case the hair was cut very short in order that the scalp might be washed more thoroughly.

*Case 12.*—A.W., a girl, aged fifteen, had had eczema on her neck, cubital spaces and fingers since infancy. She also had perennial hay fever, and the family history was positive for atopy. Urticarial reactions to scratch test: ragweed pollen, + + +; human dander, + +. Eczematous reactions to patch test: (on normal skin) human dander, +; (on scarified skin) human dander, + + +, and E.M.Z. eczema scales, negative. No definite improvement attributable to dander avoidance. She co-operated poorly.

*Case 13.*—Mrs. C.H., a woman, aged twenty-two, had had eczema on her face and neck since infancy, only during cold weather. It left in summer but recurred in the fall. She also had had definite vesicles on the right thenar eminence, which may have been an irrelevant condition. She had mild perennial hay fever. The family history was positive for atopy. Urticarial reactions to scratch test: dog dander, +; human dander, + +. Eczematous reactions to patch test: (on normal skin) human dander, negative; and E.M.Z. eczema scales, negative; (on scarified skin) human dander, + +, and E.M.Z. eczema scales, + + +. She had been rid of eczema for many months when her husband returned from overseas. Five days later the eczema recurred on her face and neck. The husband had unusually large amount of dander on his scalp. The eczema persisted for three weeks and was present when she left the city. No further notes are available.

*Case 14.*—Mrs. J.A.M., a woman, aged thirty-six, had had eczema since early childhood. When first seen, the lesions were present on the face and on the neck down to the dress line, where a sharp margin separated the lesions on the neck from the normal skin covered by the dress. The left upper extremity was entirely free of lesions but the right cubital space and adjacent areas of the right arm and forearm were involved in a severe eczematous reaction. This woman had the habit of invariably sleeping on the right side with the right arm in contact with her forehead. The family history was negative for atopy. Urticarial reactions to scratch test: human dander, + + +; foods and inhalants, negative. Eczematous reactions to patch test: (on normal skin) human dander, negative, and E.M.Z. eczema scales, negative; (on scarified skin) human dander, + +, and E. M. Z. eczema scales, negative. This woman was told to wear a long sleeve on the right arm day and night, to wear a short sleeve on the left arm and to sleep on the left side with the left arm in contact with the forehead. After twenty-seven days the right arm and forearm had almost entirely healed and the left arm and forearm had become eczematous, but not to the same extent as the right arm had been 27 days before—in fact, the left was involved only about 5 to 10 per cent as much as the right had been. Two months later both upper extremities had only traces of eczema, but the face and neck were only moderately improved.

#### RESULTS

Clinical evaluation of the results of treatment in this disease is admittedly hazardous. There are many factors, both known and unknown, which cannot be controlled in the home, and this statement is true also regarding hospital treatment. Periods of improvement lasting only a few

days to a week were considered to be of no significance but were regarded as being merely natural variations in the clinical course of the disease (having causes, of course, but causes which could usually not be identified).

Three of the fourteen patients were not allergic to human dander. As expected, none of these benefited by dander avoidance (Table I). Of the remaining eleven cases, six exhibited no definite lasting improvement; four showed definite improvement, and in one case the lesions cleared up entirely. In the four cases showing improvement but not complete disappearance of the eczema, the most persistent remaining lesions, as a rule, were those in the flexure of the cubital space.

#### DISCUSSION

From the results of these observations, together with evidence presented in previous publications,<sup>2-6</sup> it appears that in the disease, atopic eczema, human dander is responsible for part of the lesions in some cases and perhaps even for all the lesions in a small percentage of cases. It appears to be very improbable, however, that *surface contact* with human dander is responsible for (1) the persistent lesions in the four cases which showed definite improvement, (2) the major portion of the lesions in the six unimproved patients who were found to be allergic to human dander, and (3) the lesions in the three patients not allergic to human dander. While human dander is capable of causing the disease, and does cause the disease, and is, I believe, the most important *known* allergenic excitant of the disease, it is very probably not the most important *existing* allergenic excitant of the disease. The evidence, as it stands, indicates that there are one or more unidentified excitants. These should be investigated and identified if possible.

#### II. CUTANEOUS REACTIONS TO ECZEMA SCALES

In connection with the causative factors involved in the pathogenesis of this disease, the question arises, why (in any particular case and in cases in general) do the lesions involve the skin areas which they do involve rather than some other skin areas? The following theoretical possibilities were considered: (1) that involved skin areas contain a higher concentration of allergen than uninvolved areas, (2) that in involved areas for some unknown reason (flexion and extension? thinness of epidermis? perspiration? other mechanical trauma?) the allergen (not necessarily present in higher concentration) is able to penetrate more readily to the reactive tissue, (3) that involved areas are specifically more highly sensitized than uninvolved areas, and (4) that nonspecific, nonallergic factors determine the location of the lesions (related to item No. 2.).

Previous observations<sup>6</sup> indicated that involved skin areas are not specifically more highly sensitized than uninvolved areas. Attention, therefore, was directed toward other possibilities, especially toward that of the pos-

# ATOPIC ECZEMA—SIMON

TABLE II. PATCH TESTS WITH ECZEMA SCALES AND HUMAN DANDER  
A. ON PATIENTS WITH ATOPIC ECZEMA

Case No.	Age (Yrs.)	Patch on Normal Skin			Patch on Scarified Skin		
		Human Dander	E.M.Z. Scales	Petrolatum	Human Dander	E.M.Z. Scales	Petrolatum
1	1/2	++	—	—			
2	2	+	+	—			
3	3	+++	±	—			
4	1	++	—	—			
5	2	++	++	—			
6	2	++	++	—			
7	1/2	—	—	—			
8	2	++	—	—			
9	1/2	+++	—	—			
10	2	++	++	—			
11	1/2	—	—	—			
12	3	±	+++	—			
13	3	+	+++	—			
14	2	+++	++++	—			
15	1	++	—	—			
16	2	+++	++	—			
17	17	—	—	—	+	—	—
18	12	—	—	—	+++	—	—
19	13	—	—	—	+++	—	—
20	11	—	—	—	+++	—	—
21	9	—	—	—	+++	+	—
22	36	—	—	—	+++	+	—
23	22	—	—	—	+++	+	—
24	26	—	—	—	+	—	—

## B. ON NONECZEMATOUS CONTROLS

1	2	±	±	—			
2	1	±	—	—			
3	1	—	—	—			
4	1	—	—	—			
5	2	—	—	—			
6	3	—	—	—			
7	32	—	—	—	—	—	—
8	21	—	—	—	—	—	—
9	41	—	—	—	—	—	—
10	15	—	—	—	—	—	—
11	18	—	—	—	—	—	—
12	20	—	—	—	±	+	—

sible presence of allergen in the lesions. This was done even though previous attempts to discover detectable quantities of human dander allergen in the lesions (of atopic eczema) had met with failure.<sup>6</sup> A search was being made for allergens other than the human dander allergen. Several patients were tested with their own eczema scales. The tests were made on uninvolved skin areas by scratch, patch on normal skin and patching on scarified skin.<sup>5</sup> These tests were all negative. Tests were then made on one patient with eczema scales from other patients. Approximately 200 tests were performed with eighteen different scale specimens. While most of these tests were negative, it was found that the eczema scales from certain patients possess the property of producing eczematous reactions to patch tests (on normal unscratched skin) on certain other patients with atopic eczema. Furthermore, eczema scales from different patients possess this property in varying degree. The scales of one patient, E.M.Z., a thirteen-year-old child with severe, almost generalized, atopic (?) eczema, possessed this property to somewhat greater degree than the others. Table II shows the results of patch tests with E.M.Z.'s eczema scales.



The scales were mixed with sufficient petrolatum to make a thick paste and applied as a patch test with adhesive tape in the usual manner. The patches were allowed to remain in position two days. Readings were made several hours to one day after removal of the patches. The reactions consisted of papules, papulo-vesicles, redness, slight swelling and later slight crust formation and desquamation. The mild reactions lasted three or four days. In one case they remained distinctly visible for three weeks and in another case for four weeks. The stronger reactions were typical areas of eczema, indistinguishable from other naturally occurring lesions on the patient. Twenty-four eczematous patients were tested. Sixteen were less than four years of age. Eight of these gave positive reactions to patch test on normal skin. Eight were more than nine years of age. Three of these gave positive reactions to patch on scratch test. Of twelve non-eczematous controls, ten gave negative reactions, one a questionable reaction and one a slightly positive reaction (Table II).

#### DISCUSSION

The lesions of certain cases of atopic eczema were found to possess eczematogenous properties and evidently contain an eczematogenous agent. This agent is not a primary irritant, as shown by negative reactions to patch tests on noneczematous persons; it is probably an allergen. Its chemical nature and biologic origin are undetermined. A study of Table II shows that the reactions to E.M.Z. eczema scales do not parallel those to human dander. (Note especially Cases 9 and 12.) Hence, the allergen of these scales is not identical with the human dander allergen.

The etiological significance of these reactions is unknown. The implication, however, is that the lesions themselves contain an etiologic agent of the disease. This agent may possibly have its origin in some micro-organism or it may arise in the epidermis itself as the result of some antigenic modification of cell substance as the cells are pushed outward from the *stratum germanitivum* toward the *stratum corneum*.<sup>1</sup> In this connection several questions arise, among them being the following: Why did E.M.Z. give negative reactions to her own eczema scales while certain other patients gave positive reactions to these scales? A possible answer to this question may be that E.M.Z. is relatively less sensitive, and certain other patients relatively more sensitive, to an allergen present in high concentration in E.M.Z. eczema scales and present in lower concentration in eczema scales of certain other patients. Questions of infection arise. Tests must be made with sterilized scales. Needless to say, much work remains to be done.

#### SUMMARY

1. Eleven of fourteen patients with atopic eczema were found to be allergic to human dander. Diminished contact with human dander was followed by (a) complete disappearance of the lesions in one case, (b) definite improvement but not complete disappearance of the lesions in four cases,

(c) no definite improvement in six cases allergic to human dander nor in three cases not allergic to human dander.

2. Scales of the lesions of certain patients with atopic eczema were found to possess the property of producing eczematous reactions to patch test on other patients with the disease. Eczema scales from different patients possessed this property in varying degree.

Patch tests performed on twenty-four patients with the most reactive scale specimen resulted as follows: (a) on sixteen children less than four years of age, tested on normal skin, eight were positive and eight negative; (b) on eight persons, nine to thirty-six years of age, tested on scarified skin, three were positive and five negative. Controls on ten noneczematous persons resulted in one slightly positive and one questionable reaction.

Patch tests performed simultaneously with human dander on the same twenty-four patients (and on the controls) indicate that the eczematogenous agents of human dander and of atopic eczema scales are not identical.

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## SENSITIZATION TO PETROLATUM IN OINTMENT BASES

(Continued from Page 583)

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SEPTEMBER-OCTOBER, 1948

## RAGWEED DERMATITIS

### Therapy by the Oral Route

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**R**AGWEED is but one of more than a hundred plants which may cause dermatitis of the allergic contact type. While it may present the picture of acute dermatitis seen after exposure to poison ivy, oak, or sumac, the usual clinical picture is that of a chronic dermatitis.

Because of the fact that many plants cause dermatitis, Sulzberger<sup>1</sup> feels that "it is almost certain that dermatologists as well as allergists must from time to time see and fail to recognize contact dermatitis caused by weeds."

The eruption is usually distributed on the exposed surfaces of the body, such as the face, neck, forearms, hands, legs and feet, and may become generalized.<sup>2</sup> The condition is not hereditary, and those who acquire the dermatitis from the ragweed plant do not suffer from hay fever or asthma. There is no naturally acquired immunity, the tendency being to suffer more severely on each subsequent occasion.

The first reported cases appeared in 1918. In 1928 it was established that the exciting cause of the dermatitis was the oleoresin of the ragweed plant and pollen. At this time it was found that the patch test was the only method of confirming the diagnosis.

The important factor in the diagnosis is its seasonal incidence and recurrence, the symptoms appearing in August and ending with frost, corresponding with the period of pollination of ragweed. However, symptoms may appear as early as May, when the ragweed plant begins to grow, and may continue well up until November, as the ragweed plant maintains its vitality until that time. Contact with the withering plant is possible until it is rotted by the snow. Ragweed seed in the ground may cause symptoms all winter if handled.

Symptoms may be present at other times, such as while hunting, weeding, or handling hay or grain. The symptoms may also be continued by exposure to pyrethrum, turpentine, vegetable oils, and industrial sensitizers.

#### CASE HISTORIES

*Case 1.*—L. W., aged forty. The dermatitis first appeared in August, 1940, while the patient worked as a gardener. The eruption was generalized, as far as he can remember, and lasted all year. He has had similar episodes each year since, beginning about the same time of the year, in May, and lasting until after the first of the year. He is usually free from symptoms from January to May.

There is no history of personal or familial allergy. Turpentine fumes and rainy weather cause exacerbations.

Read at the third annual meeting of the American College of Allergists, Atlantic City, N. J., June 6-8, 1947, by Dr. Francis, chief of the allergy clinic of the Rochester General and Highland Hospitals.

Dr. Slater is associate director of the Eastman Kodak Company, with which Dr. Norris and Dr. Francis are also affiliated.

The patch test with ragweed oil was markedly positive. It was removed two hours after application because of intense itching. This patient took ragweed oleoresin orally in 1946. His skin was normal that year.

Case 2.—L. B., aged fifty-three. The patient was well until late summer of 1938 when he developed eczema of the hands, scrotum, legs, and face. He was seen by a dermatologist, who found him very sensitive to ragweed, goldenrod, and metallic silver. The condition cleared in the early winter, to recur in October, 1939, clearing considerably in mid-November, but not to a degree permitting normal activity. It became much worse in October, 1940, and at this time, because of its persistence throughout the preceding year, it was thought that the patient might be sensitive to some of the chemicals with which he was working. There was a positive patch test to one of these. On November 1, 1943, there was a very severe flare-up of dermatitis, following a hunting trip and a garden clean-up, when tomato vines were handled. In January, 1944, he reported that merely his presence in the workroom caused his face, neck and arms to burn, smart, and itch. He had been taking oral ragweed antigen for some months, but he did not wish to continue. An acute flare-up frequently occurred following incorrect dosage. His work was shifted to another area where the material used involved only dry gelatine, but the eruption persisted. The occupation was changed to water purity control where the only possible exposure might be to infinitesimal quantities of chlorine. The most acute exacerbation occurred, however, in September, 1945. The patient went to the mountains, where he improved very promptly, and was nearly well when he returned home a month later.

The condition flared up promptly again, so that hospitalization was necessary. He returned to work on December 10, 1945, still with considerable chronic eczema. This persisted, especially on the legs, during the following winter and spring, becoming worse in July. He spent August, September and October in the Adirondacks, returning to work November 4, 1946. He has been very much better since that time, even though working in an area where he had previously had trouble. The face and trunk are nearly clear, the only area remaining active being on the legs. It is proposed that he return to the mountains during the ragweed pollen season.

#### RAGWEED DERMATITIS ORAL DESENSITIZATION

##### I. Etiology.

###### A. Predisposing causes.

1. Older males (twenty-eight to seventy-four).
2. Farmers.
3. Season: July to frost.
4. Not hereditary.
5. Long exposure.
6. Hunting.
7. Weeding.
8. Handling hay and grains.

###### B. Exciting cause.

1. Ragweed—ether extract of pollen or leaves (if patient is sensitive to one weed, he is usually sensitive to all of its botanically related members).

##### II. Symptomatology.

- ###### A. Early symptoms consist of red, tender, edematous lesions of eyelids and neck, spreading to other parts of the body by hands, clothing, and the application of greases.

- ###### B. Aggravated by wind—better with rain.

- ###### C. Average eruption is three months—July to frost.

## III. Pathology.

- A. Subacute inflammatory reaction of type seen in chronic eczema or dermatitis.

## IV. Diagnosis.

- A. Positive ragweed test confirms diagnosis.  
 B. Negative test to:  
 1. Pyrethrum  
 2. Turpentine  
 3. Potassium (arsenite 1 per cent)  
 4. Corrosive mercury chloride (1 per cent)

## V. Treatment.

- A. Wet dressings, lead acetate and Burow's solution, soothing baths and drying lotions.  
 B. Change of environment.  
 C. Desensitization, oral.  
 1. Total amount required: at least 2 c.c. of ether extracted plant oleoresin.  
 2. Administration: ingestion of 30 c.c. each of 1:100, 1:50, and 1:25 dilution in corn oil (provides approximately 2 c.c. of oleoresin extract).  
 3. Time: two to eight months, depending on "tolerance" of patient.
- | <i>Dilution</i> | <i>Amount</i>  | <i>Time</i>  |
|-----------------|--|--------------|
| 1:100           | 1 drop.  | Daily—7 days |
| 1:100           | 2 drops  | Daily—7 days |
| 1:100           | Increase to tolerance until dilution is exhausted.                     | Daily        |
| 1:50            | One-half the number of drops of 1:100 dilution increased to tolerance. | Daily        |
| 1:25            | One-half the number of drops of 1:50 dilution increased to tolerance.  | Daily        |
4. Intolerance symptoms: pruritus ani, exacerbation of dermatitis.

## DISCUSSION

These cases are of interest because they show the importance of recognizing ragweed dermatitis when it occurs in industry, since this type of dermatitis is not usually compensable. In the first case (L. W.), the seasonal incidence and recurrence of the dermatitis corresponds with growth and pollination of ragweed, and the diagnosis is substantiated by a positive patch test to the oleoresin of ragweed. In the second case (L. B.), it appears that ragweed is the primary cause of the dermatitis, with continuation of symptoms best explained by other factors, some of which may be related by exposure to industrial sensitizers.

## TREATMENT

At present, the best advice to give a patient who is afflicted with ragweed dermatitis is to go to a place where ragweed does not grow. If this is not possible, the treatment of choice is by oral desensitization, using the ragweed oleoresin in corn oil. According to Rudolf Baer, this may be a safe and effective method of desensitization for ragweed, and it has also been shown to be an effective method in some cases of poison ivy dermatitis. However, one must always be on the alert for intolerance of the ragweed oleoresin, which may produce an acute exacerbation of all the symptoms.

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# Editorial

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*The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.*

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## POSSIBLE DANGERS IN MILD SHOCK THERAPY

The administration of pollen extract is, in general, a procedure which is not attended with any acute danger or repeated injury to the patient. However, in the experience of the editor, many allergists, following a certain school of thought in regard to therapy, increase the dose to just below the level of shock. Indeed, in certain clinics in this country reports of experimentally induced "mild" anaphylactic shock in patients undergoing therapy is reported with little thought of damage to the patient.

Recent experiments by Castberg and Schwartz\* should lead those of us who are responsible for the welfare of the allergic patient to pause and take stock in the laxity of the recommendations often advised for allergic therapy. Castberg and Schwartz show that in five young hay-fever patients, following a shocking dose of pollen extracts, there were important changes in the electrocardiograph. In all cases, changes typical for anoxemia of the myocardium were found.

Although there was no evidence to suggest any specific allergic reaction in the heart and although the authors believe that changes depended upon decreased ventilation of the lungs, our attitudes in this case must be specifically connected with the welfare of the patient. Just what, for example, is the effect of overdosage over prolonged periods, for many years? Do doses producing subclinical shock in the tissues lead to chronic changes due to therapy? In view of the fact that this question cannot be answered, it appears desirable at present, to cautiously avoid shocking doses of allergens or doses of allergens beneath the shocking level in the therapy of hay fever and asthma.

## EXPERIMENTAL TUBERCULIN SENSITIVITY

It has been known for a number of years that the immunological specificity of the tuberculin reaction is associated with a protein of *M. tuberculosis*, which has been isolated and studied in considerable detail. Such tuberculoproteins have proven in large scale tests to be proper reagents for tuberculin testing "PPD" of Seibert. Tuberculoproteins are true antigens. Animals injected with it form antibodies which give typical test tube reactions, and animals can be anaphylactically sensitized, but the delayed local and systemic reactions which characterize tuberculous infection could not be experimentally obtained. In the latest issue

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\*Acta Medica Scandinavica, Vol. 126, 1947, page 459.

of *The Journal of Infectious Diseases* (82:267, 1948), S. Raffel presents in detail the evidence which shows that delayed sensitization of the tuberculin type can be obtained in the guinea pig, if tuberculo-protein is given in admixture with the wax of the tubercle bacillus. By further fractionation of the wax, the activity was found to be associated with esters of hydroxy fatty acids with carbohydrates and higher alcohols, which have first been studied by Anderson. (This fraction also contains the "mycolic acid" which causes the acid-fastness of tubercle bacilli.) Both local and systemic reactions of the delayed type were produced in the guinea pig by the mixture of protein and wax. The characteristic toxic reaction of the explanted bone marrow of sensitized guinea pigs was also obtained with these mixtures. It appears that the wax modifies ("directs," as Raffel puts it) the antigenic effect of the protein. The mechanism of this "directing" activity is unknown, except that in a negative way it can be stated that it is unlike the adjuvant action of paraffin oil and related substances.

Beyond the high factual interest of these observations, their impact on our conceptions concerning allergy of the delayed or "infectious" type is bound to be considerable. Raffel mentions unpublished data which showed a similar modifying influence of the wax on unrelated antigens, e.g., egg albumin. A new rationale for experimental approach to problems of supersensitivity seems thus to be opened.

### FOOD SENSITIVITY IN ASTHMATIC CHILDREN

Hill<sup>1</sup> states: "That food can cause asthma in children is a fact beyond dispute. The frequency of this sensitivity, as well as its relative importance to recurrent respiratory infection, sensitization to pollens and other environmental allergens, is an entirely different question, concerning which there is considerable difference of opinion."

This thought-provoking paper brings into sharp focus the necessity for careful interpretation of positive food tests in asthmatic children, for Hill finds that only about 20 per cent of the positive tests are of clinical significance. It emphasizes anew the need for complete evaluation of all factors involved in skin testing. One must not conclude that food sensitivities are of no significance, however, but attention must be paid to the fact that sensitization to pollens and other environmental allergens are perhaps more frequently of greater significance than is generally thought.

Hill deplors the use of elimination diets, and this warning is well given, for children subjected to restrictions may suffer serious nutritional difficulties. He states: "Positive tests to foods have the same significance as positive tuberculin, trichophyton or brucellergen tests, namely—that at some time the organism has been exposed to antigenic material and an immunological reaction, which may or may not have anything

to do with the clinical condition under consideration, has occurred." In line with this thought, Ratner and Untracht<sup>2</sup> have shown that children, at one time highly sensitive to egg white both clinically and by skin test, may retain a residual skin reactivity years after their clinical sensitivity has worn off.

Hill's paper clearly demonstrates the importance of the careful evaluation of skin tests. It should make us conscious of their limitations, but it should not lead us to disparage the skin test, nor to curtail the number of tests performed. Rather, the relative importance of each positive reaction should be carefully appraised in the light of all accumulated findings in the individual case.

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## RAGWEED DERMATITIS

(Continued from Page 596)

### SUMMARY

1. Two cases of ragweed dermatitis were presented.
2. Both were treated by the oral method, using the ragweed oleoresin in corn oil.
3. One patient was symptom-free for a year. The other patient had to discontinue treatment because of intolerance.

We gratefully acknowledge the photographs by Miss Merlynn Cook, A. B., which were presented originally with this paper.

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Medical Department  
Kodak Park



# Progress in Allergy

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## MISCELLANEOUS ALLERGY

### A Review of Recent Literature

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In reviewing allergy literature during the past year, the impression has again been gained that much effort is being utilized in the search for newer methods and approaches to measures that will insure more exact diagnostic possibilities and more definite expressions of benefit. The review of last year<sup>40</sup> was arranged in a fashion which grouped the various phases of allergy together and excluded those subjects adequately covered by other writers. This seemed to be the most satisfactory manner for a presentation of a review of this type, particularly when there are so many specific instances which could easily be a part of the other reviews dealing with sectional material. Again, the reviewed material is being presented according to the following outline: (1) General, (2) Respiratory, (3) Dermatological, (4) Gastrointestinal, (5) Headache, (6) Infection, (7) Histamine and Antihistaminic Preparations.

#### GENERAL

More attention during the past year has been paid to the close association between the allergic picture and the precipitation of these symptoms by emotional disturbances and responses. Abramson<sup>1</sup> points out the lack of communication between two journals, one devoted to the study of allergy and the other devoted to the subject of psychosomatic medicine. During a period of seven years, the latter publication presented twenty papers relating specifically to the emotional problems of the allergic state, while the former journal had only one brief report on the same subject. He feels that too much emphasis has been placed on the histamine theory in an effort to explain the allergic phenomena. Abramson further states that several publications have dealt chiefly with this theory but only a few have been directed toward the basic explanation of "why" the histamine theory does not answer all the questions involved. He presents several interesting cases in which the diagnosis of allergy was very definite, but in whom the mechanism of their symptoms was specifically aggravated or initiated by psychodynamic forces. Patients are also described in whom the allergic symptoms were not proven to be immunologically allergic. He calls for two steps that seem necessary for fundamental advance in the specialty of allergy.

Editorials and contributions of an allergic nature should be sought and published by the journals dealing with psychosomatic material, and contributions designed to emphasize the role of emotional factors in the allergic patients should be encouraged by the editorial staffs of the allergy journals. This author also points out that the early recognition of anger and hostility as influencing factors upon the allergic paroxysm had its origin in the time of Hippocrates.<sup>2</sup>

Mitchell et al.<sup>3</sup> have decided that a basic re-evaluation must be made of the generally accepted allergic etiology in those groups of patients discussed in their article. In the "reacting" group of patients, the incidence was noted to be about equally divided between the sexes. In the "non-reacting" group, there was a noticeable predominance of females, with the majority of patients being in the third, fourth and fifth decades. The authors could not explain this variation on a basis of

allergy and the speculation is made that the difference lies in the personality factors and adjustments that are most common within the home circle. The realization that confusion, fear, hostility, family or office troubles and the like are of marked importance has led them to the more satisfactory diagnostic and therapeutic approach resulting in their ability to help patients in whom they had previously experienced failure. Of 100 cases of perennial asthma, 21 per cent were considered psychologically maladjusted in view of the expressions of confusion, guilt, fear and hostility made in the initial history interview. Metzger<sup>65</sup> considers neurotic factors to be frequently of considerable and primary importance in patients complaining of allergic symptoms. The allergist, and the psychiatrist as well, must be aware of the possible aggravation of allergic symptoms and emotional disturbances by either specific sensitization or fears and fixed ideas.

Chemical factors in asthma have been very adequately reviewed by Wiswell and Rackemann.<sup>112</sup> They state that though vitamin deficiencies are not the likely causative factors of asthma in any instance, such deficiencies may aggravate an asthmatic state already present. Other factors—blood sugar, calcium, phosphorus and magnesium—remain unchanged usually in the asthmatic individual and therefore no relationship can be demonstrated. The acid-base balance is of importance because of the excessive  $\text{CO}_2$  which may result from insufficient pulmonary ventilation, and thus cause increased dyspnea. Though there is no indication that electrolyte and water balance changes are directly effective in asthma production, a marked shift may aggravate or improve the asthmatic complaints. Coca<sup>18</sup> made a study of the antiallergic effect of sympathectomy and sympathetic ganglion block. He has demonstrated the weakness of histamine injections as contrasted with the selectivity of sympathectomy. Cases are presented in evidence and the effect of ganglion block may be of sufficient duration to forecast the antiallergic effect of sympathectomy. Kline<sup>53</sup> considers the tissue changes in allergy under five headings: functional, inflammatory, proliferative, degenerative, and necrotic. The functional changes bear no detectable morphologic alteration of cells. Allergic reactions are stated to be characterized by rapid onset, violent course and slow regression! This certainly is characteristic of the patient with severe seasonal hay fever! This author considers the tissue changes in allergy to reflect the severity of the signs and symptoms of the reactions, even though some animals in anaphylactic shock fail to reveal any appreciable morphologic change of sensitized smooth muscle. Various methods of testing for drug sensitivity have been outlined and discussed by Hansen-Pruss and Leeper.<sup>50</sup> Skin testing, not always accurate in this determination, offers several possibilities. Passive transfer testing by injection of serum supposed to contain the antibody is followed by oral administration of the drug. The drug then would be subject to the processes of digestive metabolism and might stand a good chance of producing a positive reaction at the site of serum injection.

Recurrent parotid swelling occurring shortly before the onset of asthmatic attacks has been described by Waldbott and Shea.<sup>113</sup> The elimination of offending foods produced relief from both parotitis and asthma. The fact that the parotitis may occur for many years prior to the onset of asthma should influence all practitioners to the prediction of asthma with the presence of undetermined parotitis as of allergic origin.

Active allergy as a common cause of growth failure has been described and presented by Cohen and Abram.<sup>20</sup> They were able to follow 150 allergic children in private practice and determine that the frequency of allergy is more marked in the slender, constitutionally adapted male child. They discuss a grid method whereby the growth failure of these allergic children may be followed and frequently be detected. Immunity based on antibody formation has been presented

as a specific type of resistance in that the lymphocyte has a definite relationship to immune globulin production. White<sup>109</sup> feels that the adrenal cortex is one of the most important hormones involved in immunity production. Editorial policy has outlined the difference between cumulative and non-cumulative dosage plans.<sup>33</sup> The former involves the administration of small doses repeated at such intervals as to cause a final tissue concentration sufficient to produce the therapeutic effect desired. The non-cumulative method requires the administration of a single dosage effective in itself after the complete elimination of the previous amount. Some drugs require many days for the cumulation of effectiveness, while others may have the so-called side effects presented by single dosage administration. Proetz was unable to find any association between the severity of symptoms of vasomotor rhinitis and the basal metabolic rate.<sup>79</sup> Thirty-seven of eighty-four patients were improved on thyroid therapy, though thirty-four were known to have definite hypothyroidism.

Randolph<sup>82</sup> has continued his very interesting studies of the blood in allergic states. The original work of leukocyte changes following the trial feeding of foods was extensively studied by Vaughan. This author has done well in continuing the impression of eosinophilic changes and their importance. He has shown that the postingestion eosinopenia which occurs simultaneously with the production of allergic symptoms is identical with the response of the blood and the clinical picture observed in drug allergy. Many patients will develop a delayed eosinophilia which is noted to be in evidence as the clinical picture is found to be subsiding. This response is not commonly noted during the first hour after the ingestion of food or drug. Single or repeated feedings in normal persons were found to be not followed by a constant variation in the eosinophile level.

Eighty-six per cent of over 1,500 patients showed negative reactions to intradermal skin tests with iodopyracet. Alyea and Haines<sup>5</sup> found that, of these 14 per cent positive reactors, thirty-four of them experienced the general type of reaction. Their findings have shown that the patient with a positive family history, a personal history and positive skin test reactions to diodrast is most likely to have a general reaction to the drug. The warning is given, however, that the physician using the drug should be on guard for the unusual patient who will present systemic reaction symptoms with no previous indication of allergy in self or family. The ability of the adrenalectomized rabbit to produce antibodies has been the source of study for Murphy and Strum.<sup>70</sup> Such production seems to result from a hypertrophy of the lymphoid tissue and prevention of the adrenal cortical hormones does not reduce this indication. In fact, there was no difference between the titers of hormone-treated and hormone-untreated operated rabbits.

The standardization of both pollen and dust extracts has been the source of discussion and experimentation over a period of the past several years. There have been many interesting and erudite articles published on the subject and each seems to include the plea to all allergists for support in the contention that extracts must be placed upon an acceptable standard before satisfaction can be reached. Extract standardization has been the particular interest of the American College of Allergists. The Standardization Committee of the College has published their report upon the various methods used for the standardizing of allergenic extracts.<sup>87</sup> Evidence is thoroughly presented to show that there is no relationship between the skin reactivity and the total nitrogen present in an extract. Nitrogen is considered to be a poor method of standard in view of the variation in the molecular size of the various antigens—in this instance, dust. Extracts whose antigens are of the same molecular size (and when adjustment is made for the phosphotungstic acid precipitate nitrogen—different from total nitrogen—so that this factor was constant) were productive of somewhat more constant degree of skin reactivity with less over-all error. A successful standardization of dust extract, therefore, can only be reached by a combination of chemical and biological methods. The ideal

extract gives a positive reaction on a clinically known sensitive patient, and a negative reaction on the normal control individual. Rimington and his associates<sup>53,54,55</sup> feel that the antigen in the house dust extracts used by them was only a very small part of the total material. They preferred heated fractions of the extracts to those prepared by Seitz filtration because of the stronger intracutaneous reaction produced by the former. They felt that this might be due to the lack of filtrable viruses destroyed by heating. They have also worked with mold extracts and found that in their patients no positive reactions were determined for mold extracts in association with negative dust reactions in that patient. Wodehouse<sup>56</sup> discusses the various methods of pollen extract standardization and describes each in some detail. By comparing two apparently similar grass pollen extracts, this author has found a difference in their reactive potency by neutralization of reagin at local passive transfer sites. The extent of the neutralization has been revealed by retesting these sites with standard pollen extracts. This reviewer is of the opinion that the standardization of allergenic extracts upon a basis acceptable and usable by practicing allergists is the outstanding challenge to the specialty today.

#### RESPIRATORY

It is often found that the drug or method of therapy used to obtain relief in one patient will cause alarming and untoward symptoms in the next. Greenblatt<sup>57</sup> has reported the use of Pristine hydrochloride in the treatment of rhinitis in a patient two months of age. About thirty minutes after the installation of a few drops of the 0.05 per cent strength of the solution, the patient was found to be lethargic, and markedly stuporous. The symptom-picture was noted for about three hours, after which a very gradual and uneventful return to normal was experienced. This same author has reported to this reviewer<sup>58</sup> two similar instances occurring with the same drug, though not in the same method of application. Hainesworth<sup>58</sup> cites his case in which the patient noted almost immediate symptoms following the swallowing of about 3 to 4 c.c. of 0.1 per cent Pristine. Unconsciousness eventually was quite profound. After a rather stormy period of hours, a return to normal was reported. Sensitivity to powdered sulfonamide compounds has been reported by Ballenger<sup>59</sup> when he describes the use of this type of medication application in 1,500 patients. Of these patients, to whom over 6,000 treatments were given, only seven experienced some type of evident allergic reaction to the drugs. Good results were noted in the abatement of the infectious processes and a definite lessening in the percentage of complications.

Over the period of the past few years, there has been a rapidly spreading interest shown in the use of radium application to the nasopharynx in the treatment of both chronic infectious and allergic states. The radium can be purchased outright for use or can be rented by the practitioner for use in his limited number of patients. Either method of obtaining the material is somewhat expensive, but results seem to indicate the justice of such procedure. Findlay<sup>60</sup> treated forty cases of nasal polyposis over a period of seven years. Insertion of the radium applicator followed a submucous resection and an exposure of the ethmoid labyrinth. His results showed that only four recurrences were experienced and there were no complications of any consequence. That irradiation of the nasopharynx is the treatment of choice for infectious or allergic conditions is expressed as the opinion of Crow.<sup>61</sup> A recurrence of lymphoid tissue following the removal of tonsils and adenoids in children is often given as the basic causative factor for the onset or aggravation of a bronchial asthmatic state. Radium or radium application has been successful in the control of this complicating or etiologic condition. Stansbury<sup>62</sup> in an unpublished series of similar cases has been quite enthusiastic about the results and the absence of complications with the use of the radium applicator. The technique of administration has been described by various authors and the reader is

referred to the various articles dealing with the use of the applicator. That surgical removal of adenoid tissue often is not adequate has been the basis of a report by Proctor.<sup>78</sup> In the process of repair following the surgical procedures, lymphoid tissue is present in the stroma of the mucous membrane serving as a replacement. As a result of infection or allergy, or a combination of the two, this lymphoid tissue is seen to grow rapidly and in good proliferation with an aggravation of an established bronchial asthma or an addition to an already or continuing nasal symptom-complex. This paper reports good results in 400 patients who received 1,100 radon treatments as adjunctives to the usual nose and throat measures. It has long been recognized that the simple removal of tonsils and adenoids will not benefit the average allergic patient, either nasal or asthmatic. Sixteen of thirty-four children reported by Ward et al<sup>107</sup> had had surgical removal of the tonsils and adenoids without lasting benefit. With recurring infections, severe asthma was noted regardless of the removal of exciting extrinsic causes. Complete disappearance of lymphoid tissue from the nasopharynx was seen in twenty-three of the thirty-four cases following the use of radon application on four occasions spaced at monthly intervals. Associated results showed that fifteen of these patients were completely relieved while eight of the twenty-three had a marked diminution in the frequency and severity of their attacks. Fuels and Almour,<sup>42</sup> on the other hand, traced specific instances of deafness to the ingestion of fish, tomato, tobacco and powders. They propound that since epinephrine 1-1,000 subcutaneously was of benefit in the relief of the acute deafness, the basic pathology must have been a hydrops of the perilymphatic space causing impairment of auditory function by exerting pressure on Corti's organ.

Though the subject of seasonal hay fever is sufficiently large in practice and in literature to comprise a review in itself, it is felt that there may be instances wherein the nature of the material would justify its inclusion in this miscellaneous review. Certainly this is true of the mold studies that have made good progress in recent years. Mitchell et al<sup>68</sup> report the symptom of vulvo-vaginitis pruritus occurring as a major part of ragweed sensitivity in eight patients. Their patients were all children and responded exceedingly well to hyposensitization measures. The eight cases are presented in brief form and they give the impression that though this complex is relatively rare, seasonal vulvar itching is rather common in particular groups. The age of onset was under five in seven of twenty-four hay fever cases and between five and ten years of age in only one of fifty-five cases. They predict that the condition will probably not be encountered beyond adolescence. Each patient has his own individual level of pollen tolerance, whether it be in the nature of symptom production by inhalation or injection in therapy. Rackemann<sup>50</sup> discusses the work of previous investigators and presents several cases to show that good results can be obtained with a small series of extract dosages if the correlation is made between the amount per injection and the level of tolerance for that particular patient. It is always easier to obtain a better, more satisfactory, result in the treatment of hay fever in the second or the third year of therapy than in the first. Rackemann feels that this is due to the study of the patient's response to various dosages in previous years, which should always be used as a guide in the management of the seasonal hay fever in subsequent years. In this way, the level of "absolute tolerance" can be determined, and as long as the pollen dosage remains beneath that reactive level, no general reactions will be experienced from therapy. It should be emphasized, however, that that level may vary from patient to patient, and in the same patient from year to year. It has been this reviewer's thought that this reactive level may vary in the individual patient in the same year from time to time, and that this variation may be due to the amount of exposure or the rate at which the pollen extract is being supplied to him in therapy. It is

brought out that there is a discrepancy between skin test reaction and clinical sensitivity and that there is a "constitutional" factor in hay fever which is quite apart from local cellular antibody. It is admitted that better results should be gained by experience with the same patient in successive years of therapy, but some determination must be made for that original year. It has been noted by this reviewer that the patient who has a poor result his first year of treatment is the reluctant patient in subsequent years, and usually falls back on non-specific measures for anticipated relief. Skin test reactivity or skin titration with various dilutions of pollen extract seems a more reliable method of dosage determination than first year at least, than does the guess and hope system. Rooks<sup>44</sup> has reported an all-glass cylinder to which is fitted a top and bottom of plate glass. The precipitating electrode is of platinum wire. The collecting electrode is a Petri dish through the center of which is inserted a copper rivet. The medium is poured to a sufficient depth to cover this rivet. He has found a very marked increase in the sampling efficiency by electrostatic precipitation as compared with impingement of the fungus spores. In a series of collected articles,<sup>32,69,76,98</sup> Prince and his co-workers have reported on their recent investigations with mold extract preparation and studies. Twenty-nine *Alternaria*-sensitive patients were tested by scratch and intracutaneous methods with extracts of frozen, unwashed, lyophilized pellicles of *A. tenuis* and *Aspergillus niger*. Extracts prepared from washed pellicles were compared. No significant difference in skin reactivity could be determined in the *Alternaria* extracts. Patients clinically sensitive to *Aspergillus niger* were somewhat difficult to select, so the majority of comparative testing was done with the *Alternaria*-sensitive patients and extracts. The skin reactive fraction of the *Alternaria* extract tended to remain within the cellophane bag used in dialysis. It was suggested that the enzyme activity of the mold preparations altered the permeability of the cellophane to interfere with dialysis. Dutton found that treatment with mold extracts gave exactly the same results as the use of pollen extracts in the pollen-sensitive patient. Constitutional reactions were obtained with mold extracts in higher dosages and some patients experienced accentuation of their asthmatic symptoms while under therapy with comparatively high dosages. Morrow points out the "top ten" group of genera for all collecting stations to be *Alternaria*, *Hormodendrum*, *Penicillium*, *Aspergillus*, *Pulularia*, *Torula fusarium*, *Trichoderma*, sterile pale species and sterile dark species. She also reported that each station had a consistent "big six" which varied from station to station but were still listed in those mentioned above. The "top ten" should cover most of the testing for most of the men interested in allergy. Sellers feels that desensitization therapy with mold extracts is definitely worth while.

#### DERMATOLOGICAL

Ehrlich<sup>34</sup> adds to the discussion as to whether light urticaria is a genuine allergy or whether it is only a photodynamic phenomenon. Sulzberger and Baer<sup>102</sup> are quoted by Ehrlich as having obtained a positive passive transfer and ascribing the urticarial sensitivity as due to the presence of reagin in the blood stream. This is in support of the allergic theory for light sensitivity. Further discussion is given by this author to heighten the breach between those men of allergic inclination and those in support of the photodynamic theory. Ehrlich presents a case report of a patient having had itching and urticaria on exposure to sunlight over a period of ten years. Symptoms were less severe in winter than in summer, but were present in perennial fashion. A fluorescent lamp failed to reproduce the lesions, as did various other forms of artificial sunlight. Passive transfer studies in his patient were successful. Rubin et al<sup>91</sup> found that patients could markedly increase their tolerance to light with Pyribenzamine.

One of the most therapy-resistant conditions seen in the allergist's office is the

patient presenting himself with lesions characteristic of fungus sensitivity. No single method of therapy is successfully applicable to these patients and even when an apparent benefit has been found, subsequent remissions are the rule rather than the exception. The secondary lesions are usually of much greater severity and a source of much more discomfort than the primary focus. A large amount of fungus sensitivity is being seen today, and this may be stated to arise in the number or the type of infections that resulted from military service in various parts of the world. It is recognized that the secondary "id" lesions are of allergic origin and should respond to immunologic management. Sensitization is one of the primary factors in the development of these secondary lesions. These authors present thirty patients who have been followed over one year. Jaros and Kirsner<sup>53</sup> found associated allergy in 56.7 per cent of their patients. In an attempt to hyposensitize these patients, a dilute extract was chosen in order to avoid reaction symptoms in the most sensitive instances. If a dosage of more than 0.2 c.c. was used local necrosis was noted and best results were obtained with an amount of 0.1 c.c. at twice weekly intervals. Injections were given intradermally. After an average of 22.5 injections, results are reported as 93.3 per cent showing improvement with 40 per cent of these being classified as cured. This reviewer has used a plan somewhat similar to that described by these authors and has met with similar good results. Often the average patient with evidence of fungus sensitivity has been around to so many and varied types of therapy that he is reluctant to assume further time and expense in an apparently fruitless search. With such encouraging results as reported by Jaros and Kirsner, the outlook for some patients would seem much brighter.

Cohen and Kaufman<sup>19</sup> have found that, in four cases of penicillin urticaria, Procaine hydrochloride intravenously was successful in two patients. They point out the danger of possible sensitivity to the drug and warn against its use in indiscriminate fashion. The use of Procaine intravenously for the relief of the arthralgia and myalgia calls for a solution made up of 1 gram Procaine to 500 c.c. of physiologic saline. These writers report in detail the two instances in which Procaine was a failure under their management. In the discussion it is remarked that many forms of therapy were used without avail, and recovery was spontaneous and prolonged. No mention is made of the use of histamine intravenously, which preparation has met with almost astounding success in the relief of penicillin reactions of this type. An ampoule (1 c.c.) of histamine diphosphate of a strength 2.75 mg. (representing 1 mg. histamine base) added to 250 c.c. physiologic saline has relieved the majority of such reactions seen by this reviewer. It is felt that the administration of the histamine must be given in sufficient amount, strength and rate of flow to produce a mild flush. Prince<sup>77</sup> spoke on this at some length in the discussion of his paper in Oklahoma City.

A very interesting and worthwhile symposium on eczema-dermatitis has been published by Sulzberger, Tolmach, Hill, and Simon. The clinical picture of eczema is described by Sulzberger<sup>103</sup> as being characterized by erythema, edema, papules, vesiculation, oozing, weeping with subsequent thickening, lichenification, pigmentation and itching. He explains the different features and the reasons for such differences between so-called allergic eczema, numular eczema, seborrheic eczema and many others in which the morphologic changes are due to mechanisms other than immunologic. The recognition of a contact type of dermatitis indicates the prognosis and therapy. Therapy must consist of removal of contact or a reduction in the degree of contact with the determined causative agent. Local therapeutic measures must be appropriate, and no reliance can be placed upon the use of antihistaminic agents. Tolmach<sup>106</sup> feels that the allergic individual is not more easily sensitized than is the non-allergic worker. He explains the difference between "obvious" and "insidious" primary irritants. Simple protective measures will correct a dermatitis due to simple irritation, but true allergic dermatitis calls for a change in the oc-

cupation or the type of occupation for the employe. In infantile eczema, the removal of the suspected or proven offending food or environmental substance combined with proper dermatologic treatment will usually give a satisfactory end result. Environmental allergens are more important than foods in the older child. Hill<sup>52</sup> states that the probable reason for disappointment in the management of the older child's eczema is due to the lack of proper environmental control at the same time that the attempt is made to hyposensitize the patient to the offending environmental allergen which reaches the skin through inhalation or direct contact of some sort. Simon<sup>55</sup> has used scratch and intracutaneous tests, as well as patch, patch-scratch and inunction testing to obtain reactions to human dander in the sensitive patient with negative reactions in control cases. He finds that scales from certain patients possess the property of producing inflammatory reactions when applied to certain other patients with eczema. Twenty-four patients with eczema were tested with the scales of one patient which had proven to be exceedingly active and productive of reaction. The degree of positive reaction was higher in the use of these particular scales, forcing the conclusion that a small amount of allergen formed in the proper location of the skin produces a more marked effect than a greater amount of allergen obtained by ingestion or contact.

#### GASTROINTESTINAL

In a rather thorough review of the available literature, few articles in the past year have dealt specifically with the gastrointestinal tract. Those few, however, were of interest and should be included in this miscellaneous section. In three presented cases, the diagnosis of gastritis was made by gastroscopy. Afendoulis<sup>3</sup> found that the changes were essentially the same as those found in idiopathic or infectious gastritis with the exception that the onset is more sudden. The appearance of the membrane is one quite similar to other forms of gastric upset. Causative factors were determined to be drugs or food and observation was made following the ingestion of the substances. He feels that the reaction is due primarily to the direct action of histamine or similar substances upon the membrane. Chobot<sup>17</sup> presents a timely discussion and review of gastrointestinal allergy in a very interesting article. Most common adult symptoms are abdominal distress, burning and flatulence. In true allergy, the symptoms may be reproduced at will. Gastrointestinal allergy in children is usually evidenced by colic, pylorospasms, cyclic vomiting and vague abdominal pain. Whey, containing albumin, is the chief offending fraction of milk sensitivity. Pruritus ani, as an allergic state, has been mentioned by Pearson<sup>72</sup> and Whitney<sup>100</sup>. The effect of Benadryl upon gastric acidity is the presentation of Doran.<sup>30</sup> There seems to be some disagreement as to whether the antihistaminic drugs are in opposition to the production of gastric acid or whether the effect is one of neutralization if present in any degree. When first introduced, the drug was indicated to be suppressive to gastric acidity but since that time changes of opinion have been published and digested. Langley and Smyth<sup>56</sup> and Seibold<sup>25</sup> are other authors who have discussed food allergy and allergy of the gastrointestinal tract. The latter article was found to be well worth while and instructive in all phases. Rudolph and Sage<sup>92</sup> feel that there are two groups of patients with allergic problems referable to their digestive systems. The first group is comprised of those in whom the symptoms and reactions are exceedingly slight and may be easily overlooked or incorrectly diagnosed. The second group is made up of those patients with evident associated allergic states and in whom the digestive symptoms are recognizable as a part of the allergic affair. These authors draw upon their military experience and the cases that were seen during that time. It is their impression that the detailed history is of primary importance in the diagnosis of gastrointestinal allergy. In any event, thorough gastrointestinal studies must be



done. The presence or absence of skin test reactions is not the deciding factor alone in the diagnosis of an allergy affecting the digestive system. The accurate completion of a food diary is an essential feature that should not be overlooked for, by this means, the physician is able to determine the time and association of the symptoms with the causative, offending substances. Treatment when possible should be directed toward the elimination of the etiologic factor or factors with resultant hyposensitization and dietary routine. This reviewer has met with little or no success in the few attempts made to hyposensitize for foods. The elimination of the food has been found to be the only satisfactory means of successful therapy. Patient tolerance will determine whether he may use little, some or none of the causative substance without the production of symptoms. Nor has this reviewer been able to place a burden of responsibility for diagnostic accuracy upon the question of a positive or negative skin test in the search for the answer to gastrointestinal allergic conditions.

? "Food allergy should be considered as a cause of fever when the physical examination and laboratory studies give no explanatory clues and especially when treatment based on positive findings gives no relief." Such is the opinion of Rowe.<sup>90</sup> He has presented a very complete case study in which the allergic fever was of the persistent type and was present daily for four and one-half months of hospitalization. The degree of allergy to the causative foods can only be determined by feeding tests after the complete elimination of excluded foods has shown a remission of symptoms. A maximum degree of allergy must be assumed until the symptoms, whatever they may be, have been relieved. The failure to consider allergy as a possible cause of otherwise unexplained elevations of temperature may account for needless surgical procedures or prolonged rest and hospitalization. The fever due to allergy is usually persistent but may be of the remittent type. It is wise to look for other manifestations of allergy which may accompany the elevation of temperature.

#### HEADACHE

Alvarez<sup>4</sup> is of the impression that migraine is a disease of the brain dependent upon inheritance for the condition. This predisposition is likely to remain throughout the life of the patient. The strain of everyday life and the psychic make-up of the individual will govern the severity and the frequency of the attacks. This author bases his findings upon a study of 500 cases, a great number of whom were of the female sex and who fit into a rather typical physical and mental plan. Because of the influence that such predisposition has, the added factor of allergy, hypertension and menstrual difficulties aggravate or initiate the migraine seizure. Alvarez feels that the most effective form of therapy consists of rest, reassurance, and the elimination of factors productive of tension and worry—all of which adds up to adequate psychotherapy. Symonds<sup>105</sup> and MacLaughlin<sup>60</sup> do not agree in all respects with the above presentation, but similarity can be found in their basic approach to the patient. Dixon<sup>20</sup> discusses the use of histamine in the diagnosis and treatment of headache. Boggs<sup>11</sup> also feels that intravenous histamine is of marked value if properly used and effectively administered in the treatment of the migraine attack. Goodman and Coonrad<sup>43</sup> gave 0.3 mg. histamine phosphate to 113 persons without the subjects knowing the nature of the medication. Twenty-one normal subjects failed to have a resultant headache from the subcutaneous histamine. Of thirty-four persons subject to headaches, twenty-two were histamine positive. Two of these, with a history of migraine, developed such severe attacks that measures other than adrenalin were necessitated. Following the use of 100 mg Benadryl none of these positive twenty-two persons developed a headache. Further proof of such protection was displayed in the testing of fifty-four patients whose chief complaint was headache. Thirty-one of these developed their usual headache following the

injection of the histamine, but of these, eighteen were subsequently without headache after the protection afforded by 100 mg. Benadryl. These authors feel that the majority of periodic headaches are on a vascular basis. They recommend that adrenalin be used more frequently as a therapeutic measure for relief of headache. This is based upon their experience of finding the ability of the drug to relieve the headaches induced by the injected histamine solution. They found that Benadryl was 92.5 per cent effective in preventing headache from the same dosage which previously had produced definite, and, at times, alarming symptoms in their test patients. Schnitker and Schnitker<sup>34</sup> established the diagnoses of migraine in their patients with the sublingual administration of nitroglycerin. A dosage of 1/50 grain reproduced typical symptoms which were readily relieved with oxygen inhalation, ergotamine tartrate or carotid artery compression. The reaction from the administered drug is noted within two hours. Excellent relief of severe attacks was attributed to the use of dihydroergotamine tartrate by Blumenthal and Fakler.<sup>12</sup> The drug is given in a dosage of 1 mg. Toxic effects of the drug were noted in 26 per cent but were not of sufficient severity to warrant the discontinuation of the medication. Ergotamine tartrate was found to be the most effective medication in the hands of Friedman and Brenner.<sup>41</sup> More effective than any ergotamine derivative were combinations of the drug in association with caffeine or atropine given orally and rectally respectively.

Dees and Lowenbach<sup>28</sup> have presented the results of an electroencephalographic study of eighty-five allergic children. Occipital dysrhythmia was the outstanding feature of the results. It occurred in half of their allergic patients, and this was considered to be far higher than the expected finding in so-called normal children. The presence of a positive family history seems to have a definite correlation with this high incidence of occipital dysrhythmia. It was also noted that the longer the patient had had his allergic complaints the greater the tendency for the patient to show changes in his occipital pattern. Zeller<sup>117</sup> reports the third case of temporal arteritis in which eosinophile cells were a prominent feature of the cellular infiltrate. Excision of the arterial segments led to prompt and prolonged improvement and recovery. The condition was felt to be one of diffuse arteritis.

#### INFECTION

The role that infection or focus of infection plays in the initiation, aggravation or masking of the allergic symptoms in the average patient has always been an interesting feature of the specialty. The debate between the intrinsic and the extrinsic advocates will go on with much stimulation for many years and perhaps will never draw to a pleasant conclusion. It cannot be overlooked that infection does play a role in the production of many symptoms and probably many actual diseases which, through lack of proper recognition, are today included in another field. At least they are not considered as being primarily allergic in origin. Recent opinions emphasize the striking similarity between the acute joint manifestations of acute rheumatic fever and the joint involvement of serum sickness. The most important basis for such thought rests upon the delayed time for the appearance of the complaints after the infectious process has been noted or the serum has been administered. That the incidence of allergy is three times greater in rheumatic children than among non-rheumatic controls has been the findings of Rittwagen et al.<sup>80</sup> They were able to study one hundred rheumatic children and compare the findings with one hundred patients without the manifestations of the disease. Thirty-three per cent of the rheumatic group gave personal histories of having had hay fever, asthma, or food sensitivity. Thirty-one per cent had a positive family history of allergic disease. In the control group, only 8 per cent were sufferers of allergic disease, while 10 per cent were of allergic family background. Covelti<sup>23</sup> was able to produce in rats cardiac changes resembling those of rheumatic fever in human beings. This

was done by giving rats a series of injections containing killed streptococci and emulsions of rat heart or connective tissue. A possible pathogenesis for rheumatic fever is thus suggested by the author. The production of specific antibodies which react with the antigen in the connective tissue is the basis for this opinion. Cardiac enlargement and findings of pericarditis are part of the clinical picture described in McKinley's case report.<sup>64</sup> These clinical features were recognized twenty-three days after the injection of tetanus anti-toxin to a patient who had received routine immunization procedures while in service many years previously. Pleurisy with effusion, precordial friction rubs, and cardiac pain were all present during the reactive stage. All symptoms and signs rapidly disappeared within a week's time and the heart was found to be of normal size. Recovery from that time was uneventful and without consequence.

Baggenstoss, Bayley and Lindberg<sup>10</sup> feel that there is a definite underlying basis for allergy in Loeffler's syndrome. They report the presence of eosinophilic leukocytes in the pneumonic exudate in their patient, a woman with asthma of seven years' duration. Necrotizing arteritis and phlebitis, fibrosis and giant cells in the exudate and granulomatous lesions were other histologic presentations. No lesions resembling periarteritis nodosa could be found by Ayston and his co-workers<sup>8</sup> when they injected horse serum into rabbits. Their animals were given injections of serum over periods of thirty-three days with varying numbers of injections. Both gross and microscopic examination of the tissues failed to show any evidence of involvement. Placing sterile or infected silk sutures around the kidneys by Smith and Zeek<sup>100</sup> resulted in the production of typical lesions of periarteritis nodosa. The above measure resulted in a perinephritis with subsequent hypertension after one kidney had been removed from the animals. The lesions failed to develop if the hypertension was absent. They also found an absence of lesions when they injected horse serum into rabbits. They question the theory of hypersensitivity as a factor in periarteritis nodosa in view of their conclusion that hypertension was of primary importance. The etiology, pathology and clinical picture of periarteritis nodosa are reviewed by Miller and Daley.<sup>66</sup> Almost any organ may be involved but the kidney is the chief site of affection. An elevated eosinophile count usually occurs in less than 20 per cent. The symptoms, of course, are dependent upon the location of the pathology, and no clinical finding has been consistently present. Recovery may occur with little or no residual disability. Males are more commonly affected than are females, and the third decade is the age group of predilection. Fibrinoid degeneration may be a common finding in many of these diseases—rheumatic fever, periarteritis nodosa, scleroderma, disseminated lupus erythematosus, serum sickness—but a common etiologic factor should not be considered. Baker and Pollack feel that there are sufficient essential differences between them to state that all are not on an allergic basis.<sup>11</sup> In lupus erythematosus, the vascular involvement is only one phase of connective tissue degeneration whereas periarteritis nodosa is primarily a vascular disease. Rheumatic fever can also be differentiated pathologically, because of the less extensive collagen degeneration and the Aschoff bodies. As above stated, periarteritis nodosa occurs more commonly in males, whereas lupus erythematosus is predominantly present in females. The rash of lupus erythematosus is not a reliable finding. Vascular lesions identical with those of periarteritis nodosa have been found by Bohrod in a case of tuberculous meningitis.<sup>12</sup> Inasmuch as the lesions were limited to the meninges, it has been suggested that they may have been allergic in origin, with the tuberculo-protein as the allergen and the blood vessels of the meninges as the hypersensitive reactive tissue. Tuberculin reactions were unchanged by the use of Pyribenzamine in five patients in the report by Guy.<sup>47</sup>

The production of a specific antibody by the exposure of tissues to an undigested foreign substance leads to the possibility that all types of hypersensitiveness are

upon a common basic principle. Scherago<sup>21</sup> uses the term bacterial allergy to include all types of hypersensitive reactions that may develop when the tissues are brought into contact with bacteria or their products. He discusses the five types of hypersensitivity and groups them as follows: anaphylaxis, atopy, tuberculin-type, Schwartzman, and heterophile toxicity. Peritonitis of allergic origin is the subject presented by Sison, Dionisio and Chavez.<sup>22</sup> Attacks of epigastric fullness, paroxysmal pain, nausea and vomiting, with ascites, encystosis and eosinophilia occurred in their patient in association with pregnancy on four occasions. Reproduction of the complaints with an injection of estrone and relief with epinephrine followed a careful clinical analysis. Peck, Siegal and Bergamini<sup>23</sup> believe that a delayed reaction to penicillin skin test is of clinical significance. They have classified penicillin reactions into four groups: serum-sickness-like reactions, contact, erythematovesicular eruptions at the site of previous fungus infections, and febrile reactions. Subcutaneous dosages of gradually increasing amounts of noncrystalline penicillin proved successful in overcoming the sensitivity to the drug in their presented case. Three times weekly, beginning with 400 units, injections of penicillin were given with each dosage being double of the previous one. When 20,000 units were given, the skin test reaction was small while a trichophyton test was markedly positive. Good clinical response without reaction was experienced with the administration of the drug in careful but highly adequate amounts. Negative reactions to penicillin were found twenty-seven days after the first negative skin test was determined.

#### HISTAMINE AND ANTIHISTAMINES

The available literature on this subject has been so voluminous, during the past few months, that no attempt will be made by this reviewer to make this section all-inclusive. In addition, the material is of sufficient importance to warrant a review dedicated to this subject without conflicting articles using required space. If one assumes that allergen-reagin interaction releases histamine, then the histamine theory for allergic reactions is sound. Histamine release may be the result of trauma as well as antigen-antibody reaction. Most antihistamine therapy is directed in one of two directions: a development of tolerance to histamine by a series of injections of histamine diphosphate or the administration of a drug that prevents the action of histamine upon the body tissues. It has been noted that the term "desensitization" should not be applied to the use of histaminic therapy. Feinberg<sup>24</sup> has stated that attempts to demonstrate the achievement of histamine tolerance have been inconclusive. He feels that the effectiveness of histamine in allergic conditions has been exaggerated and that desensitization to histamine is not the basis upon which beneficial results are obtained. To the best knowledge, the antihistaminic drugs are effective by competing with the liberated histamine in their attachment to the receptor cell. It should not be assumed that the flood of new drugs on the commercial market will extend to the patient any prolonged degree of protection nor will they be productive of any degree of immunization.

Curry<sup>25</sup> evaluates the use of histamine and histaminase. Histamine has been used as a diagnostic agent in the determination of gastric function. Its therapeutic value rests in its ability as a vasodilator. Histaminase has not lived up to the promise of the early reports. This same author found that the degree of bronchoconstriction was in close correlation with the dosage of histamine administered to patients with varying degree of asthma.<sup>26</sup> Measurement was by means of vital capacity. The results, however, varied with each individual patient and the severity of his allergic complaints. The bronchoconstriction was more rapid in onset following intravenous administration than by intramuscular injection. Control patients failed to respond significantly after either route had been used for the injection of the histamine. Rutin was found to protect guinea pigs sensitized to horse serum from anaphylactic shock but failed in protecting normal pigs from sufficient doses of

histamine.<sup>81</sup> The authors do not theorize as to the action of the rutin in affording its protection. Mayer is of the opinion that the "competitive theory"—antihistaminic substances compete with histamine in certain enzyme systems—is sound and is supported by the fact that relationship exists between the degree of histamine sensitivity and the patient response with antihistaminic preparations.<sup>61</sup> The following experiments were performed: sensitization of fifty-four guinea pigs with horse serum, twenty pigs sensitized with hog serum, and sensitization of guinea pigs with substances of low molecular weight. It was found that it was possible to prevent or suppress all manifestations of vascular sensitivity with moderate and nontoxic dosages of Pyribenzamine.

Aerosolization of antihistaminic drugs was effective in combating the bronchospasm from histamine aerosols in guinea pigs. Feinberg et al.,<sup>88</sup> in a series of well-controlled experiments, found that the maximum duration of the protection was sixty minutes. Drugs varied in their ability to afford protection—one milligram Pyribenzamine per kilogram was the smallest amount required to give ten-minute protection to all animals and the duration was four to six hours; Histadyle or Thénylene in 3 milligram dosages gave protection for three and one-half hours while Decapryn protected the experimental animals for four hours in a dosage of 5 milligrams. Less of the drug was required when the route of administration was by aerosol than when intraperitoneal injection was made.

That the whealing capacity of the skin to histamine was unimpaired with histamine azoprotein has been determined by Dundy, Zohn and Chobot.<sup>31</sup> They studied twenty children and twenty adults, with six of the latter showing slight improvement under this form of therapy. These patients had migraine, angioedema and allergic rhinitis, respectively. They feel that their evidence does not bear out the therapeutic value nor the immunologic specificity of histamine azoprotein. Cohen and Friedman<sup>21</sup> found that the treatment of seasonal hay fever with this same product led to disappointment, but that the results in chronic urticaria were quite gratifying. Excretion of Benadryl and Pyribenzamine in the urine was studied by McGavack et al.<sup>62</sup> It was determined that 46 per cent of the Benadryl (a single test dose was 400 milligrams) was excreted within the first 24 hours and 20.1 per cent of the Pyribenzamine was recovered in the same duration. The blood levels were slower to rise with Pyribenzamine than with Benadryl, and the levels were maintained over a greater period of time. Iontophoresis was employed by Cohen et al to test twenty patients with various dilutions of histamine in order to determine whether there would be a change in response after the ingestion of Benadryl.<sup>22</sup> Their results demonstrated conclusively that there was a well-marked cutaneous antihistamine effect. The effect was rapid in its appearance. Arbesman, Cohen and Osgood<sup>6</sup> divided their clinic patients into two groups. The first section was treated specifically with pollen extracts with supportive therapy consisting of ephedrine and similar drugs. The second section were given placebo injections, and no medication was prescribed except Pyribenzamine. Clinic patients seemed to do better on Pyribenzamine than did private patients. They recognize the value of the antihistaminic drugs in the palliative treatment of seasonal hay fever, but their results have shown that the combined method of adequate hypo-sensitization plus Pyribenzamine was the eventual method of choice. The side effects of these drugs have been reported and one wonders if the so-called side effects may not be an actual part of the drug action. Wyndham and Owens report a rather marked agranulocytosis following eight weeks' administration of Pyribenzamine.<sup>106</sup> Their patient, an elderly woman, recovered under penicillin therapy, but the neutrophilic percentage was seen to decrease from 55 per cent to 3 per cent. That the dosage of the drug is an integral part in the production of side effects was reported by Brown.<sup>16</sup> Drowsiness, nausea and insomnia were in direct proportion to the size of the dosage used to control possible after-effects of typhoid vaccine administration. One hundred and forty-four

patients were given 250 and 500 milligrams of Pyribenzamine, or were used as a control group. Acute labyrinthitis as a side effect with Benadryl medication has been reported by Swartz.<sup>104</sup> Six days after the institution of Benadryl therapy for hay fever, his patient presented symptoms which disappeared upon removal of the drug.

Eight of twenty-two patients with itching skin eruptions were reported to obtain a very satisfactory degree of relief with 2 per cent Benadryl ointment. But Perry<sup>74</sup> also reported that the same degree of relief was obtained with the ointment base without the antihistamine. It was assumed, therefore, that insufficient absorption of Benadryl was present for clinical effectiveness. Intramuscular aminophylline was used as an antipruritic agent and seven of seventeen patients experienced dramatic relief in a very short period of time.<sup>26</sup> The discomfort caused by the intramuscular injection was sufficient to bring forth the recommendation that such procedure not be used routinely for the relief of non-specific itching dermatitis. Comparative studies are reported using Benadryl, Pyribenzamine, Hetramine, Neo-Antergan, 3015 R.P. and 3277 R.P. Winter<sup>111</sup> finds that the best degree of therapy can be obtained with the use of Neo-Antergan. The dosage of the trial antihistaminic drugs was varied to determine the smallest amount affording protection but the histamine was constant in aerosol administration. The toxicity index, with mice as the experimental animals, was highest for Pyribenzamine, though all toxic levels were far above the usual dosage given for routine therapeutic protection. In ten patients with bronchial asthma, Brown, Weiss and Maher<sup>15</sup> found that excellent relief was enjoyed by one patient with Decapryn. Moderate relief in four and no relief in the remaining five patients completed this group of clinic patients. Better results were noted in the treatment of seasonal hay fever—eighteen of twenty-six had excellent relief. The total results showed about 80 per cent of all groups of patients with varied allergic complaints to have been relieved with the drug. Side effects with Decapryn are roughly those noted with other members of this group of drugs. Drowsiness was experienced by about one patient in six, but the majority of these side effects were noted in the asthmatic group of patients to whom larger dosages of the drug were given. Patient preference for Decapryn was expressed by those persons who had previously been treated with other antihistaminic preparations. Antistine was studied in 100 patients.<sup>40</sup> In dosages ranging from 200 to 400 milligrams daily, some degree of symptomatic relief was seen in 59 per cent of patients with allergic rhinitis. Thirty-seven per cent of the asthmatic patients studied showed some degree of symptomatic improvement. In comparison with Pyribenzamine, Antistine was of less therapeutic value in those instances where the main complaints were of rhinitis type. The same finding was suggested when the two drugs were compared in urticarial lesions, asthma, and generalized pruritus. Antistine was less toxic and less likely to produce unpleasant side effects than was Pyribenzamine. Benadryl and Pyribenzamine were able to relieve over 80 per cent of patients suffering from pollen rhinitis or acute urticaria of varied origin. Loveless and Brown<sup>50</sup> found Benadryl to be somewhat more toxic and liable to cause drowsiness. As with all other members of this group of drugs, asthma remained quite resistant to the administration of the medication, even though the dosage was raised to what was considered to be adequate levels. No results whatever were noted in the relief of symptoms nor lesions of atopic eczema.

An ethylenediamine derivative, Neohetramine, was studied by Waldbott and Borden,<sup>114</sup> with the finding that this drug was of relatively low toxicity. Two hundred seventy-nine patients were included in this study and were given 50 milligrams of the drug at four-hour intervals, as long as symptoms were present. A control group of 48 patients was given a placebo tablet containing  $\frac{1}{4}$  grain of phenobarbital. Ten per cent of the patients noted side effects from the trial drug with urticarial lesions and nasal complaints responding in best degree to the medication. Only 18 per cent of seventy-five asthmatic patients noted some degree of good relief.

The activity and lack of toxicity of Chlorothen and Bromothen, as reported by Litchfield and his associates,<sup>58</sup> has led to the marketing of a new antihistaminic preparation labeled Tagathen. Prolonged action, as compared with Pyribenzamine, was also noted. This reviewer has used this preparation during the hay fever season of 1948 and has found that beneficial results are experienced by patients who have found other members of this antihistaminic group to be too toxic for continued administration. Good results with Pyribenzamine in hay fever are also reported by Henderson and Rose<sup>51</sup> in a group of 138 patients. Again, the results were somewhat disappointing in the asthmatic group, inasmuch as only three of fifteen were improved, and aggravation of symptoms was noted in another three of this same classification. It was rather unusual, as the lack of similar reports will substantiate, to have one patient with migraine report excellent relief from the use of the drug. Neo-Antergan and Pyribenzamine have been clinically compared by Weiss and Howard.<sup>108</sup> They agree that hyposensitization therapy is more effective and reliable than are the drugs alone. The former drug was found to be more toxic and consequently less effective in the six groups of patients treated by these authors. Twenty-three of twenty-four cases of urticaria responded very well to the use of Pyribenzamine in a dosage of 100 to 400 milligrams daily.<sup>71</sup> Atopic dermatitis was somewhat less receptive to anticipated benefit, although the pruritus was relieved in about 50 per cent of the patients so classified. This drug was also of value in physical allergy. Pyribenzamine administration preceding skin testing was contributory toward the decrease of the size of the resultant wheal although the degree of response in this regard could not be correlated with the degree of relief reported by the patient. That the dosage of the antihistaminic compound is of primary importance in predicting the degree of relief to be anticipated has been propounded by Rose et al.<sup>80</sup> Linadryl was found to have an action similar to that of Benadryl in an effectiveness of about one-half the degree.<sup>63</sup> The drug was found to be most satisfactory in the relief of acute, urticarial lesions and with decreasing effectiveness in chronic urticaria, perennial rhinitis, atopic eczema, bronchial asthma, hay fever and angioedema. Exertion as an aggravating factor in hay fever and asthma may be partially explained by Serafini in his finding of rising blood histamine a short time after physical exercise in some allergic patients.<sup>97</sup> No significant change in the blood level was noted in normal persons under similar conditions. With varied antihistaminic preparations symptomatic relief was obtained in eighty-four of 140 allergic patients.

Criep and Aaron have reported that Neohetramine is of lower toxicity than any of the other antihistaminic preparations.<sup>21</sup> Two hundred and forty-nine patients were used for this study and a very low percentage of side reactions was noted. Eighty-two per cent of seasonal hay fever patients were receptive of some degree of benefit. Thirty-seven per cent of asthmatic patients failed to obtain any improvement or relief with the drug, but the remaining 63 per cent had variable degrees of benefit. Arbesman<sup>7</sup> has compared the action of Neo-Antergan, Pyribenzamine, Hydryllin, Neohetramine, and Antistine in 291 patients. He reported the superior effectiveness of Pyribenzamine in allergic rhinitis, with Hydryllin being of greater benefit in the asthmatic group. This drug relieved 64 per cent of forty-eight patients with asthma. The question has always been in the mind of this reviewer whether such superiority might be aided by the aminophylline (though in recognized small dosage) contained in the preparation. It has been stated that the most potent and effective of these preparations are also the most active in their local anaesthetic properties.<sup>41</sup>

Benadryl was successful in the treatment of allergy to insulin. Leavitt and Gastineau<sup>57</sup> found that the generalized urticaria in one patient and the large local flares at the site of injection of the insulin in their second patient were well controlled and markedly reduced with 100 milligrams of Benadryl. Penicillin reactions are most common in patients who have had repeated courses of the drug. Pillsbury

and his co-workers report the effectiveness of Benadryl in controlling some of the urticarial reactions from the drug.<sup>55</sup> They report fifteen cases of urticaria with the use of penicillin in eight hundred and twenty-four individuals under therapy for syphilis. Many of the reactions from the use of this drug fail to respond to any of the oral antihistaminic preparations. In almost the opposite view, Engelsler points out that the only relief with Benadryl or Pyribenzamine among his patients were those with acute urticaria.<sup>56</sup> The greatest majority of his patients with asthma or seasonal hay fever were unrelieved with these drugs, and in many instances the symptoms were definitely aggravated by the administration. Kieck<sup>51</sup> states that the use of antihistaminic drugs in the acute stage of contact dermatitis to plants and weeds has been of distinct benefit.

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## PHYSICAL ALLERGY IN DERMATOLOGY

### A Review of Recent Literature

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When W. W. Duke, the great pioneer of allergy, first used the term physical allergy, he meant allergic diseases caused by physical agents. Whether physical allergy differs basically from other types of allergy is still an open question. Formerly, the consensus was that physical allergy is not founded on an immunologic mechanism. In recent years, the study of light sensitivity especially has proved that some phenomena of physical allergy definitely are based on an immunologic mechanism. At present, it seems that various mechanisms, allergic and otherwise, are concerned in the manifestations of physical allergy.

The term "physical allergy" covers a variety of diseases which clinically resemble allergic diseases and which are caused more or less by physical agents. Physical factors play a role in many allergic conditions, other than skin diseases. This review, however, is restricted to physical allergy in dermatology.

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When we speak of physical agents, we usually mean the following:

1. Mechanical stimuli such as pressure and friction
2. Cold
3. Heat
4. Light

## MECHANICAL URTICARIA

The most common form of mechanical physical allergy is urticaria factitia or dermatographia. Severe whipping will produce a wheal in everybody. But some people are so sensitive to the touch that a slight stroking with a pencil will produce a wheal—a whitish raised area surrounded by redness. It is possible in those patients to write their name on the back of their skin by simply stroking them slightly. Hence, the name dermatographia, which means 'skin writing'. It is most likely that stroking of the skin or pressure releases some of the histamine of the skin, which in turn produces the phenomenon of mechanical urticaria.

Lewis<sup>17</sup> postulated that as a result of cell irritation caused by stroking the skin of a patient with dermatographia, the interaction of the antigens and antibodies in a patient with urticaria, or physical irritants such as heat or cold in a sensitive person, a histamine-like substance ("H" substance) was released at that particular site and was responsible for the production of the wheal. There is good evidence that this "H" substance is actually histamine. Many observations tending to substantiate the histamine theory of wheal formation have been made. Rosenthal and Minard (1939) demonstrated that histamine could be released from isolated pieces of human skin by electrical stimulation. The role of histamine in anaphylaxis and allergy has recently been reviewed by Bram Rose.<sup>16</sup> Rose<sup>22</sup> as well as Nilzén<sup>18</sup> conclude, from repeated determinations of skin and blood histamine levels, that these levels remain remarkably constant in the same person. This was also found by Haworth and MacDonald. Rose showed that in a number of patients with dermatographia, especially those showing a marked response, there is an increase in the blood histamine within five and fifteen minutes after stimulation. After twenty minutes and later, the blood histamine level often drops far below the normal value. Rose made similar observations on two cases of cold allergy and heat allergy. As yet there is no definite explanation of these phenomena. Formerly it was postulated that the histamine leaves the blood perhaps via the gastric secretion or by being absorbed by eosinophile cells in the wheal, or by some other excretion mechanism. Recently Rose<sup>22</sup> has advanced the theory that the increase of the blood histamine may stimulate the antihistaminic enzymes which may lead to a rapid neutralization of the histamine. Both Rose and Nilzén found that the histamine content of the blood of patients with urticaria or angioneurotic edema is at a very low level during an attack as compared to the level found during the quiescent stage. As far as mechanical urticaria is concerned, there is some good experimental evidence that it is caused by release of histamine. There is quite a variation in the histamine content of the skin in different persons, as shown in Table I. However, in a given person, the histamine content of the skin is quite constant.

TABLE I. HISTAMINE CONTENT OF SKIN AND BLOOD

Histamine content of skin		Histamine content of blood	
Author	8/gm.	Author	8/gm.
Nilzén	5 - 24	Rose & Browne	0.023 - 0.09
Pellerat & Murat	16 - 24	Nilzén	0.015 - 0.084

(8 = 0.001 mgm.)

Nilzén<sup>18</sup> studied the histamine content in wheals produced by mechanical stimulation in healthy individuals and compared it with the histamine content of adjacent normal skin. The results are summarized in Table II.

## PROGRESS IN ALLERGY

TABLE II. HISTAMINE CONTENT OF SKIN IN NORMAL INDIVIDUALS AFTER MECHANICAL STIMULATION

Time	Average values from Nilzén Normal skin 8/gm.	Wheal 8/gm.
2 min.	7.6	6.3
10 min.	11.5	6.2
25 min.	8.4	5.2
50 min.	11.6	11.3

There was not much difference in the histamine content of the wheal and normal skin after two minutes. But after ten and twenty-five minutes, the histamine content of the wheal dropped considerably below the values for the normal skin. After fifty minutes there was no longer any difference. These experiments indicate the release of histamine by mechanical stimulation. The same holds true for dermatographia, as is evident from further studies of Nilzén, as summarized in Table III.

TABLE III. HISTAMINE CONTENT OF SKIN IN DERMATOGRAPHIA AFTER MECHANICAL STIMULATION

Time	Normal skin 8/gm.	Wheal 8/gm.
2 min.	13.	10.3
5 min.	10.6	6.3
10 min.	16.	8.7

Urticaria factitia is different from ordinary urticaria. Many patients who suffer from dermatographia do not have any signs of urticaria, and vice versa. Still there is probably some inter-relationship because the two conditions are frequently associated. The role of allergy in dermatographism is still under discussion. Cazort<sup>9</sup> believes that positive passive transfer in dermatographism is very rare. Psychosomatic aspects of dermatographism are discussed by Dengrove.<sup>10</sup> He reports two cases in which psychologic factors seemed largely responsible. In both cases there are three factors to consider: (1) The constitutional background which reveals reacting skins in other members of the family; (2) emotional immaturity; and (3) dermatographism associated with pruritus, with the onset linked to separation from supporting persons, in one case by death of the mother, and in the other by removal from a crew to which the patient was intimately attached.

### URTICARIA FROM COLD

While most of us think that urticaria from cold is a rare affliction, Urbach and Gottlieb<sup>28</sup> state that the incidence of cold urticaria is relatively high, and that we fail to recognize it. No doubt the relation to cold may be more or less obvious. Not every exposure to cold elicits the urticaria. In some instances mechanical irritation must be added to the cold.

Cold urticaria, at least to some extent, also seems based on histamine release. As Pellerat and Murat<sup>20</sup> have shown, the histamine content of the skin decreases after freezing, thus indicating release of histamine by this process. A temporary increase of the blood histamine in patients with cold allergy fits in well with the histamine theory. At least for some cases of cold urticaria we may assume that under the influence of cold also some of the tissue histamine is released and produces the urticaria. However, it is well to remember that *it is not all histamine that wheals*. It would be a mistake to assume that all cases of urticaria from cold are based on a histamine basis. There are apparently several mechanisms possible. Rose<sup>23</sup> reported a case of cold allergy which apparently was not due to histamine.

What is the relationship between cold urticaria and true allergy? Some cases of cold urticaria give a definite impression that there is some real allergic hookup. Supporting this idea are the reports by Lewis and others of a positive passive transfer in some cases of cold allergy. What the allergen is, one cannot state at present. There are on record cases of cold sensitivity which were cured by the elimination

## PROGRESS IN ALLERGY

of focal infection or parasitic infestation. Urbach believed that many of these cases are due to functional disturbances in the vascular innervation. The antihistamines have been used successfully in urticaria from cold. Perry and Horton<sup>21</sup> found Pyribenzamine of some value in three cases of hypersensitivity to cold.

### URTICARIA FROM HEAT

Some of the considerations about cold urticaria or cold allergy apply also to hypersensitivity to heat. There are people who exhibit hypersensitivity to both cold and heat. Urbach and Gottlieb<sup>22</sup> stress the point that many cases diagnosed as cold allergy are, in fact, not due to cold at all but to the flush of heat which follows the exposure to cold. As in cold urticaria, hypersensitivity to heat may produce a local contact urticaria as well as general symptoms brought on by a reflex mechanism, which includes besides the generalized urticaria other allergic or vascular manifestations such as asthma. There is another form of heat allergy which is somewhat different. It is brought out both by exposure to heat and emotional stress. Grant and his co-workers have termed it the heat and effort syndrome; Hopkins, Kesten, and Hazel<sup>11</sup> have confirmed the findings that these cases represent a hypersensitivity to acetylcholine. The urticaria in these cases frequently does not show the large blotches of ordinary urticaria, but innumerable small urticarial lesions. Furthermore, this form of heat allergy may not even produce urticaria but just produce a pruritus. This form of heat reaction is now called cholinergic urticaria. Although a rare condition, it was extremely difficult to deal with. Some of the antihistamines counteract also acetylcholine, although this action is much less pronounced than their antihistaminic potency. Benadryl has given satisfactory results in a case.<sup>12</sup>

Sigel<sup>26</sup> studied twenty-two patients with urticaria caused by heat, exertion and excitement. All patients were American soldiers stationed in Japan. The patients with this type of urticaria constituted 2.2 per cent of all dermatologic cases seen. A sudden change of climate seemed to be of etiologic significance since most of the patients had been stationed in warm and hot climates before being moved into the temperate climate of Japan, where their first symptoms occurred. The eruption was characterized by pinhead-sized wheals, with or without erythema, and accompanied by urgent itching, prickling, and burning sensations. Symptoms were readily produced by vigorous exertion, any form of external heat or any form of excitement. There was no evidence of histamine sensitivity. Treatment in general was unsatisfactory. Burekhardt and Steigrad<sup>6</sup> present an interesting study about the effect of hot drinks on the temperature of the skin. Drinking of a glass of hot tea produced a marked increase of the temperature of the skin. The maximum was reached after four to twenty-two minutes. In order to produce this effect, the temperature of the tea had to be so high that the test person felt it as burning hot. According to the sensitivity of the test person, this meant a temperature between 42° and 56° centigrades. As similar effects were produced by drinking a glass of brandy or the eating of horse radish, the authors believe that this phenomenon is a reflex originating from the receptors of the mucous membrane. The mere presentation of a hot drink also was able to produce a reaction in the sense of Pavlov's conditioned reflex.

### LIGHT SENSITIVITY

Physical allergy to sunlight is perhaps the most complicated and also the most interesting form of physical allergy. But not all cases of hypersensitivity to sunlight are allergic in origin. For instance, there are chemicals which sensitize every skin to sunlight, the so-called photodynamic substances. The reader is referred to Blum's<sup>23</sup> book (1941). The photodynamic action of lime oil has been studied by Sams.<sup>25</sup> If people prepare a limeade and get the oil from the rind on their fingers while exposed to the sun, they all will react with a severe sunburn.

followed by pigmentation and darkening of the skin. This reaction can be produced on any skin, providing the concentration of the extract and the exposure to light is strong enough. But frequently sensitivity to sunlight is on an allergic basis. Patients may become allergic to the oil of the lime rind and sunlight. In this case, a slight exposure is sufficient to produce a severe dermatitis.

Another example of photo-allergy, as this phenomenon is called, is light sensitivity to sulfonamides. Some sulfa drugs like sulfanilamide will sensitize everybody to the sunburn spectrum of the ultraviolet, and also to the long ultraviolet and to the visible light.<sup>7</sup> This is a phototoxic reaction and can be brought upon at will under experimental conditions. However, the concentration required in the skin to produce this reaction is so high that patients receiving sulfanilamide in customary dosage do not exhibit signs of this photo-sensitivity. But there exists also a photo-allergic sensitivity to sulfonamides. Once a person has become allergic to the combination of sulfonamide and light, much smaller amounts of sulfanilamide and less light is needed to produce symptoms. Burekhardt<sup>7</sup> reports five cases of photo-allergic contact eczemas from the use of sulfanilamide ointments. Patch tests with sulfanilamide alone were negative; but patch tests with the same ointments followed by irradiation produced a vesicular dermatitis. Histologically, these reactions presented intraepithelial, lymphocytic spongiosis. This reaction was elicited both by exposure to natural sun and to filtered mercury-arc radiation which eliminated wave length below 3,000 angstrom units. Burekhardt has shown that the phototoxic, as well as the photo-allergic effect can also be produced by long ultraviolet rays, although the maximum absorption of sulfanilamide is within the range of short ultraviolet rays.

Urticaria solare is a rare condition which has attracted more attention during recent years. Beal<sup>2</sup> studied two cases of solar urticaria. Their range of sensitivity was found to be between 2,967 and 3,341 Å with a maximum sensitivity of 3,131 Å. This sensitivity could be passively transferred; positive reactions were elicited by exposing the sensitive sites to the active wave lengths. Reactions occurred within thirty minutes, and sites remained sensitive for several days. Negative results were obtained with normal control sera. The incidence of positive transfers could be increased by exposing large areas of the patient's body surface to ultraviolet light before withdrawing the blood for passive transfer studies. The serum lost most of its potency by storage at ice-box temperature for eight days. It was inactivated at 56° C. in one-half hour as well as by irradiation with ultraviolet light. The sensitizing factor did not dialyze through a semipermeable membrane. Some protection against solar urticaria was afforded by an ointment containing 30 per cent G-Salt (sodium salt of 2-naphthol-6, 8-disulfonic acid) which absorbed the rays to which the patient was sensitive. Greater protection was afforded by the antihistaminic drugs which permitted gradually increasing exposure to ultraviolet light for therapeutic purposes. This produced an increased tolerance, limited to the exposed areas which might be attributed to pigmentation and/or thickening of the horny layer of the skin. Beal believes that this type of sensitivity may result from the formation of antibodies against a physiological radiation product in the skin. Another case of urticaria photogenica studied by means of a spectrograph is reported by Burekhardt.<sup>8</sup> The maximum of sunlight sensitivity also was between 2900 Å and 3350 Å. But there was also a reaction in the range of the long wave ultraviolet at 3650 Å. Passive transfer was positive and was elicited by the same wave length which caused the urticaria in the patient. Ehrlich<sup>11</sup> also reported a case of urticaria photogenica due to wave length shorter than 3700 Å. Passive transfer was positive. His paper contains a review of the pertinent literature. Treatment of hypersensitivity to sunlight has been usually unsatisfactory. The antihistaminics have been a valuable addition, although not always helpful. The first successful report is from Tyson.<sup>27</sup> He reported prompt relief in a case of solar urticaria treated with benadryl. His

case was complicated by dysmenorrhea which, incidentally, was also controlled by Benadryl. In Burckhardt's<sup>8</sup> case Antergan lowered the erythema threshold of the patient and also prevented a clinical eruption. The sunburn protecting action of antihistaminics has been studied by Kurtin et al,<sup>16</sup> Borelli<sup>4</sup> and Baer et al,<sup>1,5</sup> Kurtin et al, were able to prevent the development of sunburn by preceding iontophoresis with Pyribenzamine. Baer and his associates<sup>33,34</sup> confirmed these findings. However, their investigations indicate that this effect is due to the "antihistaminic" action but to the physical properties of Pyribenzamine. This drug absorbs the active-wave lengths causing sunburn and therefore prevents them from reaching the skin. The absorption curve of Pyribenzamine shows a high extinction peak in the zones producing ultraviolet erythema. Baer, Kline, and Rubin corroborated their theory by additional experiments. They were able to protect the skin from sunburn reaction by placing the Pyribenzamine solution in quartz cups between the skin and the source of light, thus excluding any chemical effect on the skin. Furthermore, Benadryl, which shows no absorption within the sunburn spectrum, showed only a slight diminution of the ultraviolet erythema. However, these experiments do not exclude the possibility that there may also be some other mechanism by which the "antihistaminics" act as protection against ultraviolet. Borelli<sup>1</sup> studied the effect of oral medication of the antihistaminic drug Dimetina (dimethyl aminoethyl benzylaniline) upon the ultraviolet reaction of the skin. In the majority of cases a rise of the threshold erythema was noted. Also an increase of the latent period and a diminution of the degree and duration of the erythema. The pigmentation was less severe only occasionally. However, the subjective symptoms such as burning and itching were missing, even if they had been present and were still existing in areas that were irradiated as a control on the preceding day. Borelli concludes from his studies that a great part of the so-called antihistaminic (anti-allergic) actions of these drugs is due to their anesthetic capacity.

Niacin amide given orally produced only a slight lowering of the ultraviolet threshold in normal persons according to Burckhardt.<sup>5</sup>

The sunburn protecting effect of para-aminobenzoic acid was studied by Rothman and Henningson.<sup>24</sup> Para-aminobenzoic acid has an absorption band which embraces all the sunburn rays. As it is essentially unchanged, even after intense irradiation, is non-toxic and non-irritating for human skin, non-staining and easily miscible with ointments and emulsions, it seems well suited as a sunburn protectant for local application. The authors used 15 per cent para-aminobenzoic acid in Ruggles' cream. The protective action against the light from a mercury lamp of a 15 per cent para-aminobenzoic acid ointment in 0.03 mm. layer thickness was 50 to 100 times greater than that of the plain base. Thirty-two individuals who had complained about great sensitivity to sunshine and who had repeatedly suffered from severe sunburn reported absolute protection when exposing themselves to natural sun light. However, when sunbaths on beaches are combined with swimming, the cream had to be reapplied each time the person left the water because it is easily washed off. The authors were also successful in protecting a patient with solar herpes simplex and another patient with chronic discoid lupus erythematosus who was very sensitive to sunlight.

However, darkening of freckles and solar urticaria were not prevented by this ointment. The action spectrum of these conditions is different from that of sunburn, as shown by Felsler, Rubin and Rothman.<sup>13</sup> Besides the sunburn spectrum of about 2,900 to 3,100 angstrom units, the long wave ultraviolet between 3,000 and 4,300 angstrom units with a maximum at 3,400 units, produces a tanning effect. This "darkening phenomenon" is an immediate effect of irradiation. Felsler, Rubin, and Rothman explain the seasonal color change of freckles as an effect of this long wave ultraviolet radiation which produces oxidation and spontaneous reduction of preformed melanin granules. The long wave ultraviolet darkening cannot be

increased beyond a certain maximum. This maximum obviously depends upon the genetically determined number, size, and density of melanin granules in the individual freckles. Sunburn protectants such as para-aminobenzoic acid and tannic acid, with absorption bands confined to the sunburn spectrum do not protect against the darkening of freckles. For this purpose, substances must be used which have a broad absorption band in the range between 3,000 and 4,600 angstrom units.

The actual sensitizers are still unknown in most cases of allergic light sensitivity. The viewpoint that there is no relation between the excreted porphyrins and sensitivity to light recently has been expressed again by Orbaneja and Mendoza.<sup>19</sup> These authors isolated the porphyrins from the urine and feces in cases of epidermolysis bullosa, xeroderma pigmentosum, lupus erythematosus, erythema multiforme, erythema solare, eczema solare and hydroa vacciniforme. There was no relation between the amount of excreted porphyrins and the sensitivity to light. Patients exhibiting a high degree of light sensitivity may excrete but little porphyrin, whereas patients with a high excretion of porphyrins may be only slightly sensitive to light. Niacin amide produced clinical improvement in several cases, which was followed by an increased excretion of porphyrins. Even healthy persons who had been exposed to intense sunning at high altitude on the following day excreted up to 760 gamma of porphyrins. On the other hand, as Brunsting and Mason<sup>5</sup> state, attempts to reproduce an eruption in the skin of porphyric individuals by exposing them to sun or artificial light have been, for the most part, unsuccessful.

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(Continued on Page 626)



# News Items

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## PLEASE GIVE THIS NOTICE YOUR IMMEDIATE ATTENTION

Members of the College desiring to present the results of clinical or laboratory research, must send manuscripts, or a 250 word summary, to the Chairman of the Program Committee, Dr. John H. Mitchell, 695 Bryden Road, Columbus, Ohio, before December 15, 1948. The other members of the Program Committee are: Dr. Leon Unger, Dr. Harold Abramson, Dr. Ralph Bowen, and Dr. Lawrence Halpin.

Seventy booths have been engaged for an industrial and scientific exhibit at the Palmer House for the fifth annual meeting of the College on April 14-17, 1949. Requests for these booths have been most encouraging.

All members of the Chicago Allergy Society, as well as the Chicago Medical Society, are cordially invited to register and attend. There is no registration fee, and an attendance of 1,000 registrants is anticipated.

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Dr. F. W. Wittich was one of the guest speakers at the Fifty-Third Annual Meeting of the Utah State Medical Association on September 2-4 at Cedar City, Utah, where he presented two papers entitled, "The Importance of Allergic Diseases in Medicine and Their Basic Management" and "Emergency Treatment of Allergic Diseases." He also participated in the panel discussion on medicine.

Dr. Charles W. Bancroft of Wilmington, Delaware, presented a paper for Dr. Wittich in the latter's absence at the One Hundred and Fifty-Ninth Annual Session of the Medical Society of Delaware on September 14.

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Dr. Maurice S. Fox announces the association of Dr. George T. Raper in the practice of Allergy and Dermatology, Suite 223 American Bank Building, Vincennes, Indiana.

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The Thomas Clinic has announced its opening on September 1, at 2031 Monument Avenue, Richmond, Virginia, with practice limited to Allergy and Internal Medicine. The Clinic is continued by J. Warrick Thomas, M.D., formerly associated with the recent Graham-Thomas Clinic, and Joseph M. Hester, M.D., formerly of Bowman Gray Medical School and Baptist Hospital.

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Dr. Jonathan Forman, president-elect of the College, recently talked to the Ohio Farm Bureau (Franklin County, Ohio) on "Creative Medicine and Rural Health." He also has contributed an article on local medical history to the volume honoring Dr. Max Neurberger on his 83rd birthday.

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Doctor Forman had an article in the May issue of *The Ohio Magazine* entitled, "Health from the Ground Up."

In the current issue of *The Land*, quarterly publication of "Friends of the Land," Doctor Forman has an article entitled, "What the Doctors Can't Fix," dealing with a positive approach to health.

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## THE AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

Dr. Lyman D. Richards, president of the American Laryngological, Rhinological and Otolological Society, Inc., Dr. M. Murray Peshkin of New York City and Dr.

ANNALS OF ALLERGY

## NEWS ITEMS

Fred W. Wittich of Minneapolis were the guests of honor and presented papers at the annual meeting of the American Society of Ophthalmologic and Otolaryngologic Allergy at the Palmer House, Chicago, Illinois, October 8 and 9. This rapidly developing national allergy society now has eighty-six members and is an official member of the International Association of Allergists.

Dr. W. Byron Black, a member of the Board of Regents of the College, is president of this society and Dr. French K. Hansel is Director of the Hansel Foundation which was established February, 1947, and which has already conducted a very successful Instructional Course.

### Program

Practical Aspects of Ophthalmologic and Otolaryngologic Allergy  
(Under the Auspices of the Hansel Foundation)

*Friday, October 8, 1948*

Room 14, Palmer House, Chicago, Illinois

A.M.

- 8:00 Registration
- 9:00 "Diagnosis of Allergy from Otolaryngologic Standpoint"—French K. Hansel, M.D., St. Louis, Missouri
- 9:45 "Allergy History and Diagnosis"—Joseph W. Hampsey, M.D., Pittsburgh, Pa.
- 10:30 "Skin Testing"—W. Byron Black, M.D., Kansas City, Missouri
- 11:15 "Ocular Fatigue (Syndrome) from Food Allergies"—A. W. McAlister, III, M.D., Kansas City, Missouri (by invitation)

12:00 LUNCHEON

P.M.

- 2:00 "Pollen Survey"—O. C. Durham, Chief Botanist, Abbott Laboratories, Chicago, Illinois
- 3:00 "Prophylaxis"—Eugene L. Delacki, M.D., Chicago, Illinois
- 3:15 "Dust Therapy"—Rea E. Ashley, M.D., San Francisco, California
- 3:30 "Pollen Therapy"—Walter E. Owen, M.D., Peoria, Illinois
- 4:00 "Dietary Manipulation"—Aubrey G. Rawlins, M.D., San Francisco, California
- 4:30 "Indications for Surgery"—Kenneth L. Craft, M.D., Indianapolis, Indiana

*Saturday, October 9, 1948*

Crystal Room, Palmer House, Chicago, Illinois

A.M.

- 8:00 Registration
- 9:00 "Management of the Asthmatic Child"—M. Murray Peshkin, M.D., New York, New York
- 9:30 "Histaminic Cephalalgia"—French K. Hansel, M.D., St. Louis, Missouri
- 10:00 "The Significance of Mold Spores in Ophthalmologic and Otolaryngologic Allergy"—Fred W. Wittich, M.D., Minneapolis, Minnesota
- 10:30 "Allergic Manifestations of the Ear"—Hugh A. Kuhn, M.D., Hammond, Indiana
- 11:00 "Experience With Minute-Dose Dust Therapy"—George E. Shambaugh, M.D., Chicago, Illinois
- 11:30 "Allergy From the Ophthalmologist's Standpoint"—William D. Gill, M.D., San Antonio, Texas

12:00 LUNCHEON

P.M.

- 2:00 ROUND-TABLE DISCUSSION—French K. Hansel, M.D., Moderator
- 4:30 BUSINESS MEETING
- 6:00 COCKTAIL HOUR—Room Eleven
- 7:00 BANQUET—Crystal Room
- "Otolaryngology: Yesterday, Today and Tomorrow"—Lyman Richards, M.D., Brookline, Massachusetts

## NEWS ITEMS

The Asthmatic Children's Aid has presented a gift of \$10,000 to the University of Illinois colleges of medicine and pharmacy for investigative work in allergy.

The gift was presented to the University on July 8, 1948, by Mrs. M. Morton Strassman, retiring president of the Asthmatic Children's Aid. It was received in behalf of the University by Dr. Earl R. Serles, dean of the college of pharmacy, and Dr. John B. Youmans, dean of the college of medicine.

The Asthmatic Children's Aid has now contributed almost \$40,000 to the University of Illinois' Allergy Unit since it was established in November, 1944.

## FOREIGN NEWS

The dean of the Medical School of the University of San Francisco Xavier, Sucre, Bolivia, has invited Dr. Guido Ruiz-Moreno to conduct an Intensive Instructional Course in Allergy at this university and to co-operate in establishing an allergy service. Dr. Ruiz-Moreno has also been elected an Honorary Fellow of the French Allergy Society. Dr. Pasteur Vallery-Radot is the president of this society.

\* \* \*

We are pleased to acknowledge receiving Number 1 of Volume I, *Acta Allergologica* with the compliments of the editor, Dr. Ernst B. Salén of Stockholm, Sweden. *Acta Allergologica* is published by Einar Munksgaard of Copenhagen. The Associate Editors are Dr. Egon Bruun of Copenhagen and Dr. C. Juhlin-Dannfelt of Stockholm. Members of the Editorial Board are Doctors K. Baagøe, H. Bergstrand, P. Bonnevie, N. Danbolt, G. Dohlman, P. Frenckner, H. Haxthausen, S. Hellerström, E. Jarlov, W. Kerppola, M. Kobro, H. Malmros, Eggert Møller, U. Siirala, C. E. Sonck, Th. Thjötta, P. Blamoutier, J. Duchaine, F. J. Farrerons, W. Jadassohn, J. Liska, and U. Serafini.

The new journal contains 119 pages of investigative allergy. It is published by the Northern Society for Allergological Research, and will appear at irregular intervals, generally about one or two volumes a year. Four numbers will form a volume. The journal will publish original research work in the field of allergy, in English, French, or German, at the choice of the author.

The first issue contains an article on "État actuel de la question des anti-histaminiques de synthèse" (The Present Status of the Synthetic Antihistaminics) by Dr. B. N. Halpern; one on "Considérations sur le mécanisme de l'hypotension artérielle au cours du choc anaphylactique et histaminique chez le lapin," (Observations of the Mechanism of Arterial Hypotension during the Histamine Anaphylactic Shock in the Rabbit) by Pasteur Vallery-Radot, B. N. Halpern and G. Mauric. There is also an article on "Action préventive d'un antihistaminique dérivé de la thiodi-phénylamine sur l'œdème aigu du poumon expérimental," (The Preventive Action of an Antihistaminic Derived From Thiodi-Phenylamine on Acute Edema of the Experimental Lung) by B. N. Halpern, J. Hamburger and S. Cruchaud.

## PROGRESS IN ALLERGY

(Continued from Page 623)

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1. Hoyer, H. E: Abnormalities of the Respiratory Pattern in Patients with Cardiac Dyspnea, *Am. Heart J.* 32:457 (Oct.) 1946.

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# BOOK REVIEWS

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**FUNDAMENTALS OF IMMUNOLOGY.** Second Edition. By William C. Boyd, M.D. 519 pages. 50 illustrations, 66 Tables. Price \$6.00. New York: Interscience Publishers, Inc., 1947.

This second edition of *Fundamentals of Immunology* has been completely revised and rewritten. The rapid advances in our knowledge of immunology are adequately treated in bringing the text up to date. The basic principles of immunology in this introductory volume make it invaluable to medical students, chemists, and biologists.

Those desiring to undertake investigations in the field of serology will find the book of assistance because of the special detailed emphasis on the subject.

There are ten chapters listed in the contents: Immunity and Immunology, Antibodies and Antibody Specificity, Antigens, Cell Antigens, Blood Groups, Antigen-Antibody Reactions, Complement and Complement Fixation, Anaphylaxis and Allergy, Allergy and Immunity (Bacteria, Viruses, Parasites), Practical Use of Immunity (Artificial and Naturally Acquired), Laboratory and Clinical Technic.

The binding is durable for laboratory use, and the print and paper stock are a credit to the publishers.

**SKIN MANIFESTATIONS OF INTERNAL DISORDER (DERMADROMES).**

By Kurt Wiener, M.D. 690 pages, 400 illustrations, 6 color plates. Price \$12.50. St. Louis: The C. V. Mosby Company, 1947.

The author states that a recent systematic presentation of skin manifestations of internal disorders does not exist, and he hopes to fill this gap with the present book. It seems to the reviewer that the author has accomplished this task exceedingly well. This ambitious compilation covers the whole field in forty-three chapters. An inkling of the extent of the work put into this book may be gained by the fact that over 3,000 references are quoted. This book is both an invaluable reference book for consultation, and, at the same time, with the individual chapters well arranged, makes interesting reading.

The book is meant primarily for the dermatologist and internist, and therefore would interest most allergists. It provides easy and accessible information about the various dermatoses which are connected with internal disorders, as well as those medical disorders which present, at some time or another, skin manifestations. The allergist may be interested especially in those chapters which deal with the pathogenesis of microbids, focal infection, skin manifestations of pyogenic systemic infections, lupus erythematosus, drug eruptions, relationship of skin lesions with endocrine glands, especially the female hormones, relationship to puberty, menstruation, pregnancy, menopause, disorders of the blood and blood-forming organs, and many others. This book contains a wealth of well-presented information, part of which would be difficult to find elsewhere.

This is a book that belongs in every medical library and constitutes a valuable addition to the allergist's library.

**WANTED:** Location for the practice of allergy. Association with internist or allergist, or position in group practice desired. Have good medical background with several years' experience in allergy. Associate fellow of the American College of Allergists. Please address The American College of Allergists, 423 La Salle Medical Bldg., Minneapolis 2, Minnesota.

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\*Stillians, Arthur W.; Concealment of Cutaneous Blemishes, Arch. Derm. & Syph. 57: 279 (Feb.), 1948

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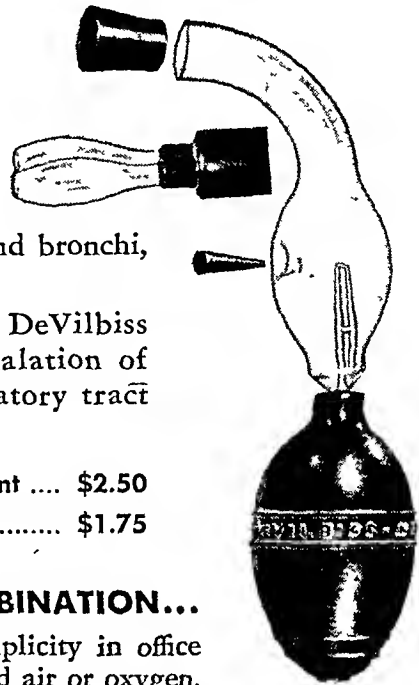
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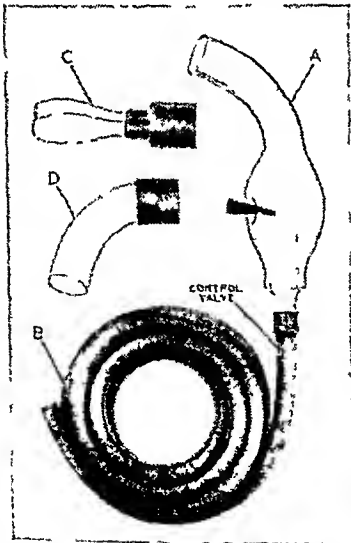
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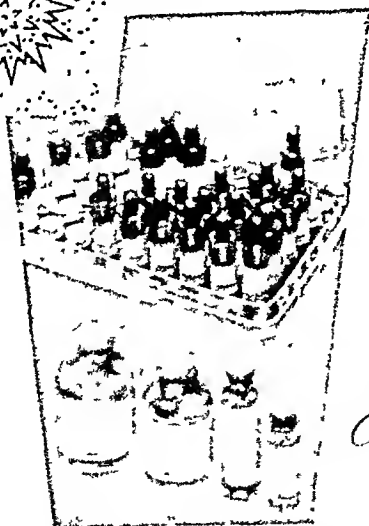
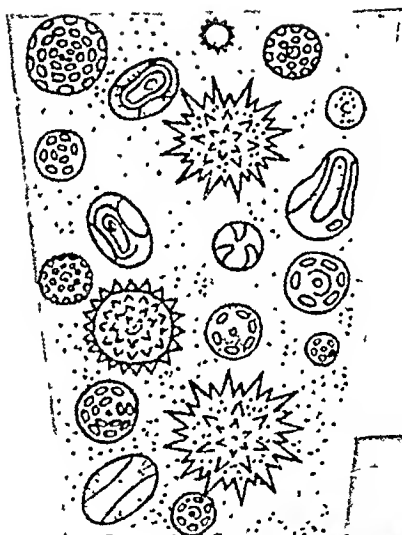


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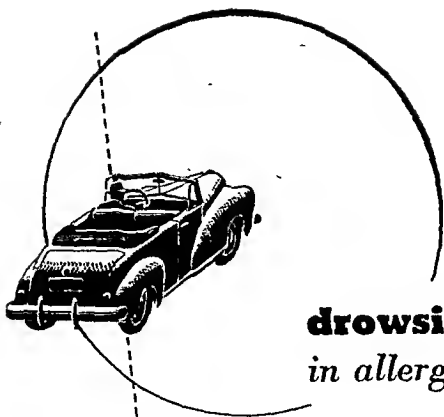


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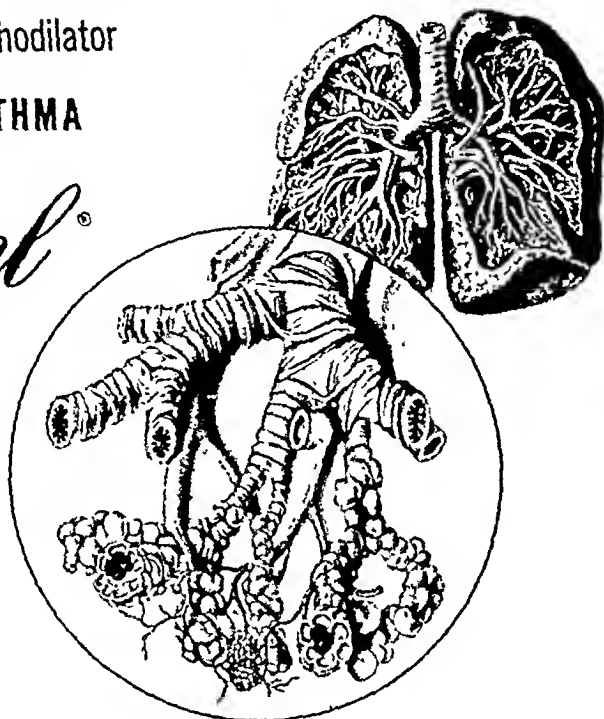
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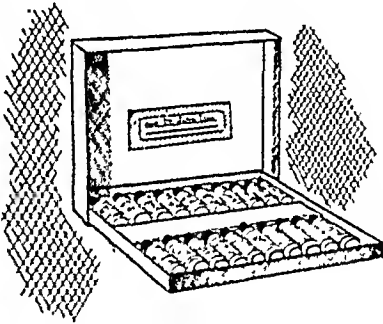
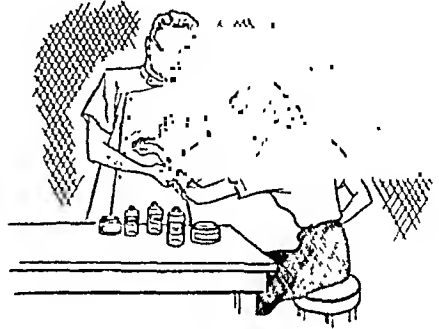
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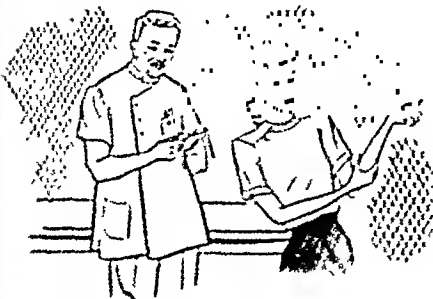
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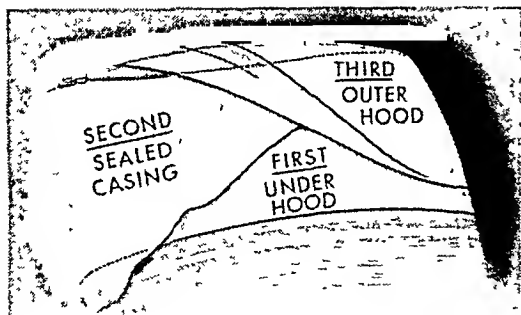
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1. Brown, E. A., et al.: The clinical evaluation of a new histamine antagonist "Decapryn," *Ann. Allergy* 6:1-6 (1948).
2. Feinberg, S. M., et al.: A new antihistaminic drug (Decapryn), *J. Lab. & Clin. Med.* 33:319-324 (1948).
3. Sheldon, J. M., et al.: Clinical observations with Decapryn, a new antihistaminic compound, *Univ. Mich. Hosp. Bull.* 14:13-15 (1948).
4. MacQuiddy, E. L.: Personal communication.

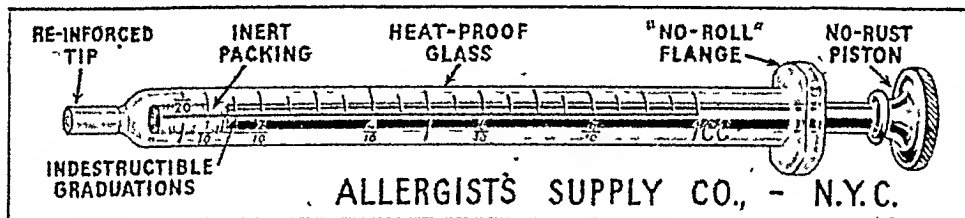
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<sup>\*</sup>Green, Arthur L., M.D., F.A.C.A., *September-October, 1948*.

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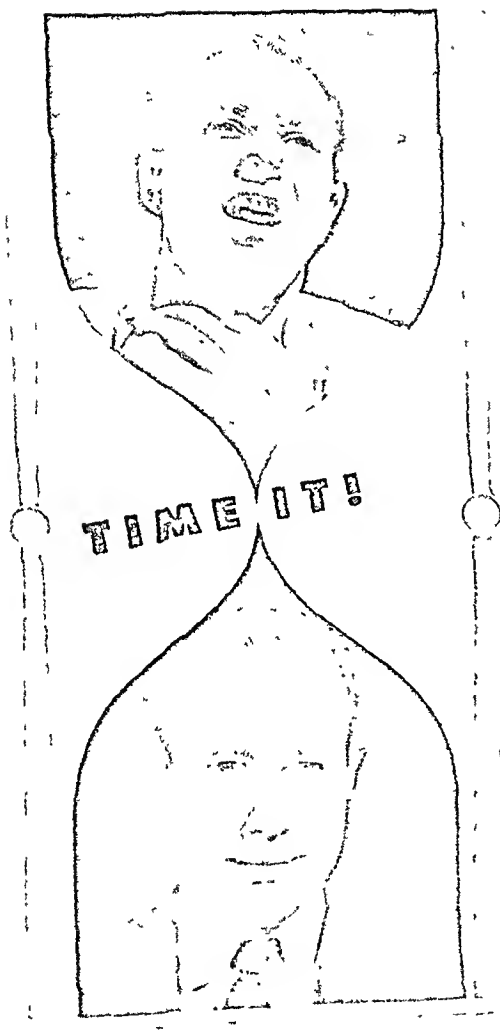
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Annals of Allergy is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, a current bibliography, editorials, case reports, new suggestions, questions and answers, news items and matters concerning the affairs of the American College of Allergists.

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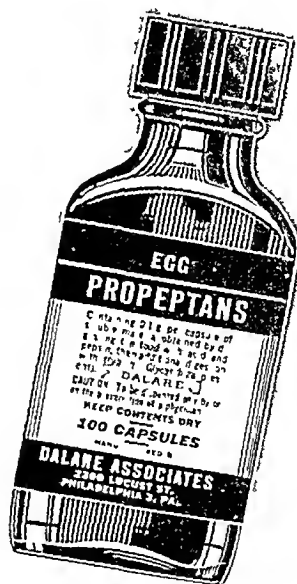
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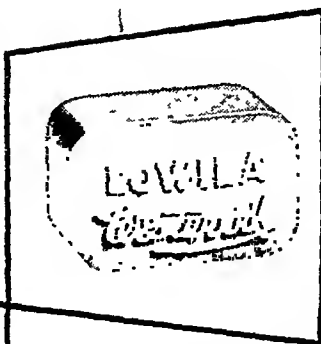
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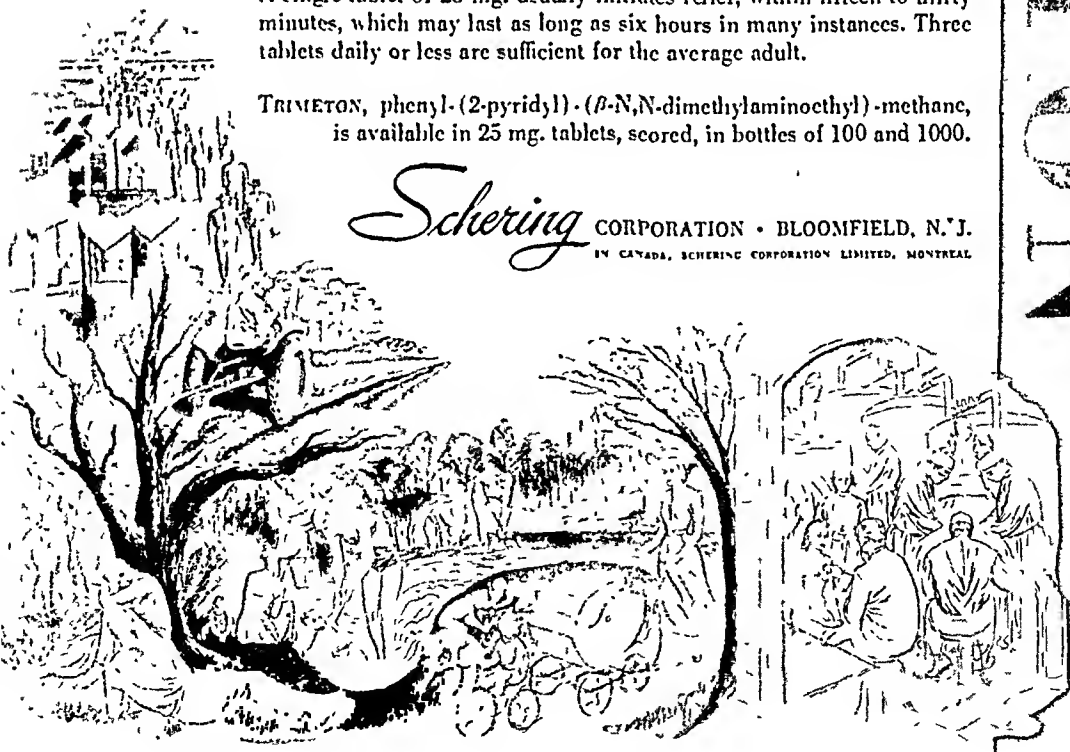
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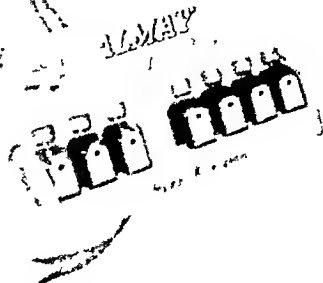
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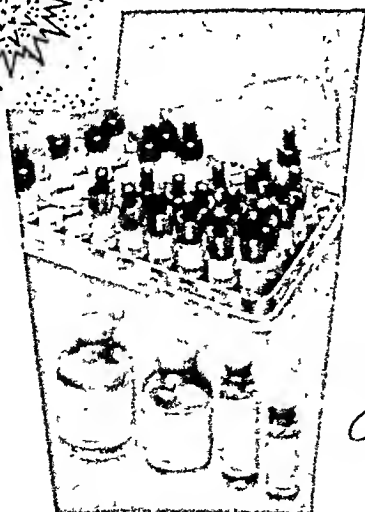
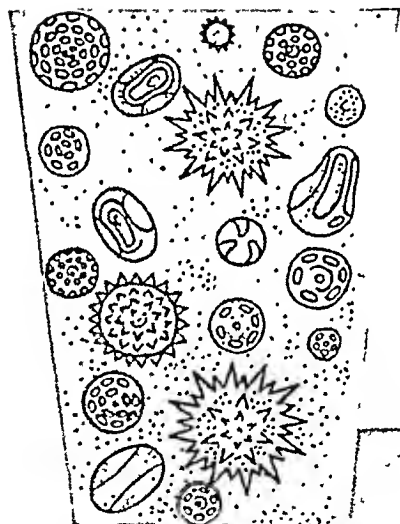


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# ANNALS of ALLERGY

*Published by the  
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Volume 6

July-August, 1948

Number 4

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## HISTAMINE DERIVATIVES WITH PROLONGED ACTION

GEORGE E. ROCKWELL, M.D., F.A.C.A.

Millford, Ohio

DALE and Laidlaw in 1910 pointed out the similarity between anaphylactic shock and the physiologic action of histamine. Since the publication of their paper, there has been an ever-increasing interest by allergists in histamine, its action, and its use in treatment. Since it is not the purpose of this paper to discuss the part played by histamine in anaphylaxis or allergy, nor to consider the advisability of the use of histamine as a therapeutic agent, no attempt is being made to survey the literature; but instead, if the reader is interested in these phases, he is referred to the work and bibliographies of: Code,<sup>2</sup> Dragstedt,<sup>3</sup> Horton,<sup>6</sup> Sheldon,<sup>10</sup> Rocha e Silva,<sup>9</sup> and an editorial on the use of histamine.<sup>4</sup>

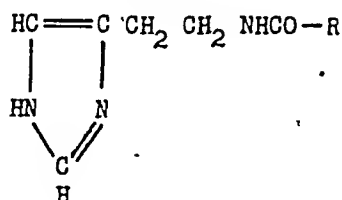
### THE PROBLEM

In the therapeutic use of histamine, it has been found advisable to give several daily injections or, as Horton,<sup>6</sup> Sheldon,<sup>10</sup> and others have done, to give it by intravenous administration. The inconvenience of several doses daily or the daily administration by the intravenous method is apparent and need not be discussed. If a preparation of histamine could be made which, when injected, had but little immediate histamine action, but slowly over a period of time liberated histamine, this would simplify histamine therapy. With this in mind, a number of preparations of histamine derivatives have been prepared with the thought that in the body these compounds would be broken down and histamine liberated slowly, or that their physiological action would be less intense than histamine but of much longer duration.

### EXPERIMENTAL STUDIES

Eighteen histamine derivatives have been prepared. Their structural formula, melting point (Fisher block), and immediate histamine-like

TABLE I. HISTAMINE DERIVATIVES AND THEIR ACTIONS



Compound No.	R	Melting Point	Immediate Histamine-like Action on 300-400 gm. Guinea Pigs When Injected Subcutaneously	Liberation of Histamine in Body†
RA 12	—CH <sub>3</sub>	149	20 mg. showed no reaction	1
RA 11 B-7	—CH <sub>2</sub> . HCL	128	20 mg. showed no reaction	1
RA 18	—CH <sub>2</sub> . CH <sub>2</sub> CH <sub>3</sub>	127	20 mg. showed no reaction	2
RA 19	—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	128—130	20 mg. killed in several hours	3
RA 28	—CH <sub>2</sub> CH <sub>2</sub> COOH	115	20 mg. no effect	0
RA 20	—NH <sub>2</sub>	120—124	20 mg. no effect	0

† 0 — none; 1 — very slowly; 2 — slowly; 3 — more rapidly.

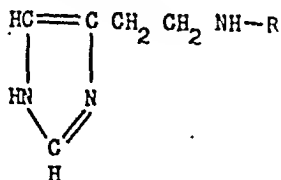
action on the guinea pig and the dissociation or liberation of histamine in the body are shown in Tables I, II, and III. Liberation of histamine in the body is estimated and indicated by an arbitrary scale, as we have no accurate means of measuring this change. In the tables under this column, "0" means no liberation of histamine; "1" means slowly liberated; "2" means a little more is liberated and a little faster than indicated by the figure "1"; and "3" means still more and faster. (These figures, instead of representing liberation of histamine in the body, may represent prolonged action.)

It has been claimed that the NH<sub>2</sub> group is the toxic group and the NH group is the anchoring group in histamine.<sup>7,9</sup> Many of our compounds have the NH<sub>2</sub> group blocked and lose their histamine action. However, this is not true in all cases, as in compounds RA-7, RA-29 and RA-30. It will be noted that they have as much immediate histamine-like action as histamine itself. Thus, attaching a radical to the NH<sub>2</sub> group does not always block the histamine action, but inactivation depends somewhat on the blocking radical.

It is not easy to attach a radical to the NH group, as when this is attempted, the aminazole ring tends to rupture. However, we have succeeded in attaching a radical to the NH group as shown in compound RA-29. In this compound it has not interfered with its physiological action.

## HISTAMINE DERIVATIVES—ROCKWELL

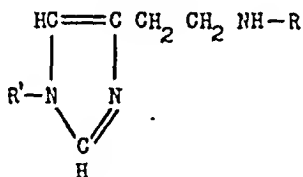
TABLE II. HISTAMINE DERIVATIVES AND THEIR ACTIONS



Compound No.	R*	Immediate Histamine-like Action on 300-400 gm. Guinea Pigs When Injected Subcutaneously	Liberation of Histamine in Body†
RA-2**	—CH <sub>2</sub> COOH	10 mg. killed 50% in 30 minutes	2
RA-21	—CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	15 mg. gave difficult breathing but pigs survived	2
RA-8	CH <sub>2</sub> CH <sub>2</sub> CHCOOH	5 mg. killed 50% in several hours	—
RA-10	CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CHCOOH	7½ mg. killed 50%	—
RA-9	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> CHCH <sub>3</sub>	2½ mg. killed in 30 minutes	—
RA-6	—CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	20 mg. killed in 1 hour	2

\* These compounds were so hygroscopic that melting point determinations were unsatisfactory.  
 \*\* The hydrochloride of this compound has also been made.  
 † 0 — none; 1 — very slowly; 2 — slowly; 3 — more rapidly.

TABLE III. HISTAMINE DERIVATIVES AND THEIR ACTIONS



Compound No.	R	R'	Melting Point	Immediate Histamine-like Action on 300-400 gm. Guinea Pigs When Injected Subcutaneously	Liberation of Histamine in Body†
RA-7	—CH <sub>3</sub>	H	*	As or more active than histamine	—
RA-30	$\begin{array}{c} \text{NH} \quad \text{NH} \\    \quad    \\ -\text{C}-\text{NH}-\text{C}-\text{NH}_2 \end{array}$	$\begin{array}{c} \text{NH} \quad \text{NH} \\    \quad    \\ -\text{C}-\text{NH}-\text{C}-\text{NH}_2 \end{array}$	182	On basis of histamine content as active as histamine	—
RA-29	H	$\begin{array}{c} \text{NH} \quad \text{NH} \\    \quad    \\ -\text{C}-\text{NH}-\text{C}-\text{NH}_2 \end{array}$	188	On basis of histamine content as active as histamine	—
RA-31	$\begin{array}{c} \text{O} \\    \\ -\text{CCH}_3 \end{array}$	$\begin{array}{c} \text{NH} \quad \text{NH} \\    \quad    \\ -\text{C}-\text{NH}-\text{C}-\text{NH}_2 \end{array}$	80	20 mg. no effect	1
RA-16	—CH <sub>2</sub> SO <sub>2</sub> Na	H	Decomp.	30 mg. no effect	0-1
RA-27	—COOC <sub>2</sub> H <sub>5</sub>	H	192	5 mg. killed in 30 minutes	3

\* Hygroscopic.

† 0 — none; 1 — very slowly; 2 — slowly; 3 — more rapidly.

## CLINICAL STUDIES

Compounds RA-12, RA-18, RA-2, and RA-21 were tried clinically. However, RA-18 was used very little as it tended to give a local reaction. RA-2 and RA-21 were most satisfactory clinically, but their use was limited due to difficulty of preparing pure preparations. Most of the cases were treated with RA-12, N-acetyl histamine.

The initial dose for RA-18, RA-2 and RA-21 was 1 milligram. This dose was increased a milligram at a time until the maximum tolerated dose had been reached. This maximum tolerated dose for RA-2 was usually from 5 to 10 milligrams.

As stated above, the compound used most was RA-12, N-acetyl histamine. The initial dose of this compound was 5 milligrams, and this was increased 5 milligrams at a time to a maintenance dose of 20 milligrams and occasionally to 30 milligrams.

While building up the doses, they were given twice weekly. After the maintenance dose had been reached, it was given once weekly. All doses were injected subcutaneously. The preparations used were a 1 or 2 per cent solution (10 to 20 mg./c.c.) preserved with 1:10,000 merthiolate, and Seitz-filtered. All solutions were cultured to be certain that they were sterile.

Seven cases of atopic dermatitis have been treated, of which four showed marked improvement and three gave doubtful or no results. In five cases of contact dermatitis, three responded satisfactorily. Nine cases of urticaria have been treated, six of which were improved. Two cases of asthma were treated with no results whatever (one was made worse). Three cases of vasomotor rhinitis were treated with no results. Three cases of migraine were treated, with two giving excellent response. One case of infantile eczema was treated with a satisfactory response. In this one case we had a histamine-like reaction, which for a few hours gave us considerable anxiety. We treated one case of Ménière's disease with partial improvement. Two cases of drug allergy were treated, one with the acetyl compound, the other with the acetic acid compound, namely, compounds RA-12 and RA-2. The results were most gratifying. Two cases of hay fever were treated with no results.

Whether these results were coincidental could not be stated. There is need of many more cases before any conclusion can be drawn. Besides the cases reported here, Dr. Harry Rogers of Philadelphia, Dr. H. R. Hoeger of Brookville, Indiana, and Dr. Paul Moore of Muncie, Indiana, have used some of these compounds. They report results similar to ours.

## DISCUSSION

The writer is inclined to agree with Horton who states, "The doctor will never know the real romance of medicine unless he has used histamine therapy." But histamine therapy by frequent subcutaneous injection,

instillation into the skin, or daily intravenous injections, is not entirely convenient or satisfactory. Therefore, if a substance could be made which, when injected, would slowly liberate histamine, then this therapy would be more simple and more available. It is possible that instead of liberating histamine slowly in the body, the results are due to the pharmacological action of these compounds. Namely, their action is not as intense as histamine and their prolonged action results because the body does not destroy them as rapidly as it does histamine. Thus, they produce a mild but prolonged histamine-like reaction.

One type of compound may be better for one disease and another for a different condition. Thus, compound RA-27, ethyl histamine carbonate, might be best suited for treatment of Ménière's disease and multiple sclerosis.

The therapeutic results of histamine therapy may not be due to the supposedly increased tolerance developed to histamine, but may be due to the pharmacological action of the drug, such as its action on the capillaries,<sup>1</sup> special vascular beds,<sup>5</sup> or the increased oxygen uptake.<sup>8</sup>

Many of these compounds are not destroyed by histaminase and, therefore, may lend themselves to oral administration.

Whether or not any of the compounds which are reported are satisfactory cannot be stated at this writing. However, it is possible that there are other compounds which would be the perfect answer to the problem.

#### SUMMARY

Eighteen derivatives of histamine have been synthesized and described as to their histamine-like action, the liberation of histamine, or prolonged histamine-like reaction. The clinical results for several of these compounds are given. It is pointed out that the therapeutic results of histamine therapy may be due to its pharmacological action and not to increased histamine tolerance. The compounds may be effective orally.

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*(Continued on Page 385)*

## PATTERNS OF ALLERGIC SENSITIZATION

ROGER P. WODEHOUSE, PH.D.

Pearl River, New York

THERE are probably well over 100 species of plants whose pollen contributes in some way to the production of hay fever and should be accounted for in attempting to control a patient's symptoms. It is manifestly impracticable for the manufacturer or the medical practitioner to maintain stocks of all, or for the latter to use so many in the diagnosis and treatment of his cases. This difficulty is generally circumvented in one of two ways, either by making up various combinations of pollens to suit the patient and the time and the place of his hay fever, or by letting one species of pollen represent a more or less restricted group of taxonomically related species. Yet it has been far from adequately demonstrated to what extent the serological relations of the various hay-fever pollens correspond to the taxonomy of the plants. Consequently it is questionable to what extent the first procedure is necessary or the second justifiable. Much useful information regarding the serological relationships of allergens has been obtained from their cross neutralizations of local passive transfer sensitizations by the Prausnitz-Küstner technique. However, recent studies by several different investigators have shown that the phenomenon is much more complicated than formerly supposed. Sera are not alike in their sensitizations; each has its own and highly exclusive reaction pattern. These patterns must be understood in order to interpret the test properly.

The test is made as follows. Sites are sensitized by the injection of 0.1 c.c. or less of the serum of an allergic patient into the superficial layers of the skin of a normal recipient. After a day or two these are reinjected with a minute amount of the allergenic material to be tested. The sensitized site reacts to its homologous allergen in about the same way that the skin of the donor of the serum reacted to the same substance. If the allergen was used in a low concentration, a second or even third reaction may be elicited at the same site, but eventually it becomes exhausted or desensitized for that particular allergen. However, it may remain active to others to which the donor was sensitive.

By means of this technique, it was long ago found that if the serum of a timothy-ragweed hay-fever case is used to sensitize the sites, when desensitized to ragweed they may remain active to timothy. Or if desensitized to timothy they may remain active to ragweed. This was interpreted to mean that the timothy and ragweed antigens were qualitatively different and that there is a specific antibody (reagin) corresponding to each specific antigen. On the other hand, if the tests with the first allergen neutralized the site to a substance of another source, and to which it would otherwise

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Read before the American College of Allergists, March 13, 1948, New York City.

have responded, the two were pronounced antigenically the same. Thus a site sensitized with the serum of a ragweed hay-fever patient was found to react freely with either the short or tall ragweeds, and if desensitized by one it likewise became insensitive to the other. This was interpreted to mean that the two ragweeds were antigenically identical. And since the tall and short ragweeds are biologically closely related, and ragweed and timothy are not, this cross neutralization was thought to be correlated with the taxonomic relationships of the pollen species. Among those less closely related, less agreement was encountered in cross neutralizations. Thus, when sites were sensitized with the serum of a grass hay-fever patient, it was found that timothy would neutralize its sites against June grass and orchard grass, and that June grass would neutralize them against timothy, but orchard grass failed to neutralize its sites against timothy. This was interpreted to mean that timothy represented the antigenic properties of all the grass family but that orchard grass was deficient in some. From these and a few similar experiments it was generalized, and almost universally accepted, that with the method of desensitization of passively sensitized skin sites, the identity or nonidentity of atopens of different origin can be determined. And those that were closely related in origin had the same or similar antigenic complex.

Perhaps the first to cast doubt upon this comfortable theory was Clarke (1927) who showed that a strong reaction of one allergen in a passive transfer site might render the site inactive on subsequent tests with unrelated allergens, the neutralization depending upon the relative strengths of the reagins of the serum. At a later date (1937) he said that when the reagin was present in a weak concentration it was subject to neutralization by almost anything, but when present in sufficient concentration so that two or more skin tests were necessary to neutralize it, no matter what was done the stronger reaction persisted.

With Sherman and Stull (1938), this concept of major and minor sensitizations emerged as their theory of dominance. They found that cross reactions depend much more upon the patient than upon the relationships between the allergens. Thus when the séra of three patients who were sensitive to dogs and cats were compared, sites sensitized with the first serum and neutralized by dog dander were found to be also insensitive to cat dander, but cat dander failed to neutralize them against dog. With the second serum the cat dander would neutralize the sites against dog, but not the reverse. And with the third serum cat and dog antigens were mutually neutralizing.

Similarly, among pollens they found that with the serum of a late hay-fever case, also sensitive to timothy, ragweed would neutralize the sites against timothy, but not the reverse. And with the serum of a grass hay-fever case, timothy would neutralize its sites against hickory, plantain, oak and sorrel, but none of these affected at all the timothy sensitization. Occasionally even one-way neutralizations were found against entirely



unrelated atopens as between horse dander and ragweed. They concluded that, "In the case of serums which reacted strongly to one antigen and less actively to several others, the most active antigen usually neutralized the serum to test with all the antigens." And, "It is apparent that the cross neutralization reactions obtained depended upon the serum tested and did not represent a constant relationship between the antigens." This they partly explain by saying that, "the reaction is analogous to the absorption of antibody by bacterial antigens." Indeed, the present report will show that the cross neutralizations among pollen species almost exactly parallels the agglutinin absorptions by the salmonella and typhoid bacteria, for example. These authors furnish a comprehensive review of the literature previous to 1938. Hence, only work subsequent to that date need be mentioned.

An interesting parallel is found among patients who are allergic to fish. Tuft and Blumstein (1946) have found that those who are sensitive to fish among the Teleostii, the group which includes practically all edible fishes, would react by skin test to fish with which they had never been in contact, even those of the Elasmobranchii, the group of inedible sharks and rays. But by cross neutralization tests it was found that the atopen of a teleost fish could neutralize the transfer sites to all fish, even to the inedible elasmobranchs, but never could the latter neutralize the sites to the edible teleosts.

Prince and Secrest (1939) showed that with the sera of some patients with hay fever in Houston, marsh elder would neutralize its sites against short, tall and western ragweed, but none of these would neutralize their sites against marsh elder. In Houston the three ragweeds (*Ambrosia*) and the related marsh elder (*Iva*) are regarded as important causes of hay fever. Obviously in some cases, *Iva* may be the major sensitization, and its antigenic structure is not identical with that of the ambrosiae.

Cooke (1944) says, "It is a common thing to find patients giving multiple reactions. Are these due to one or to many different antibodies each reacting with its own antigen?" He answers the question by showing the reactions of the serum of a patient sensitive to twenty-two different antigens; including pollens of all the taxonomic categories, orris root, *Alternaria* and *Lycopodium* spores, cotton, kapok and flax seeds. This serum was mixed with ragweed extract in sufficient concentration to neutralize it to test with ragweed, and used to prepare twenty-two sites in the skin of a normal individual. Subsequent tests showed that the ragweed had neutralized the reagin for all the allergens except plantain and sorrel.

The patient was treated with ragweed alone. It was found by a serum dilution test after treatment that the ragweed reagin was increased, as usually happens, in this case fourfold. And significantly, the reagin for plantain was also increased approximately fourfold. The author states, "This one of many such observations makes it seem probable that there is but one basic antibody unit so to speak, but with at least two prosthetic

# PATTERNS OF ALLERGIC SENSITIZATION—WODEHOUSE

TABLE I. IN VIVO DESENSITIZATION, PAR. SERUM, 1:25  
Reactions at Sensitized Sites

1st Test, 1000 units p. c.c.			2nd Test, 2000 u. p. c.c.		Reciprocal Test, 1000 u. p. c.c.		
Antigens	w	c	w	c	Antigen	w	c
Common ragweed	9	35	6	10	Sagebrush	5	0
Silvery wormwood	10	10	6	0	Sagebrush	6	0
Cabl. mugwort	8	30	5	0	Sagebrush	5	0
Green sage	11	30	6	0	Sagebrush	8	0
Coast sagebrush	13	40	7	10	Sagebrush	6	0
Pasture sage	11	25	5	0	Sagebrush	5	0

Table I. Reactions obtained at sites in the skin of a normal recipient sensitized by the intracutaneous injection of 0.05 c.c. of Par. serum, diluted 1:25, tested 4 hours later with 0.01 c.c. of each of the pollens shown in the left hand column, 1,000 nitrogen units per c.c. w = average diameter of the wheal and c = the over-all diameter of the erythema.

groups, one reacting with ragweeds and those antigens it neutralized, and another reacting with plantain." From this and the reactions of other sera it appears that, "The antibody in any particular serum when studied in detail with regard to reactions and neutralizations has what approaches a fingerprint individuality."

It would have been interesting to know if the patient with twenty-two sensitizations benefited from treatment with ragweed alone and if the benefit extended to his other sensitizations of both prosthetic groups, or if the untreated sensitizations were made worse owing to the fourfold increase of their reagins. The author points out that the blocking antibody engendered by treatment, in contrast to the sensitizing antibody, is highly specific. So much so that a patient treated with ragweed and developing a blocking antibody for ragweed, developed none for cocklebur nor for sagebrush, even though his transfer sites were neutralized for both by ragweed. If the blocking antibody is the protective mechanism, it follows that treatment with a single pollen species could only protect against the pollen of that particular species and might even aggravate the patients' sensitizations to the others.

The present study was designed to discover the antigenic structure of pollen allergens, and the correlations between their taxonomy and the patterns of their sensitization. The patterns of immunization are the subject of a study now in progress.

*Case 1.*—Par. was a resident of Los Angeles, where it appears she developed her hay fever. By direct intracutaneous tests she proved to be sensitive to most of the grasses, the ragweeds and their relatives, the Chenopods and Amaranths, the sagebrushes and mugworts. She was regarded by her physician as a case primarily of sagebrush and grass hay fever, and was being treated with a mixture of twelve different extracts representing all the main groups of pollen.

Her serum was used to sensitize six sites on a normal recipient. A serum dilution experiment had shown that this serum could be used diluted to 1:25 and still give good sensitizations. So this was the dilution chosen.

After twenty-four hours the sites were tested with extracts of the pollens of six members of the genus *Artemisia* (Table I). The reactions were recorded as the average diameters of the wheals and the over-all diameters of the erythemas. It

TABLE II. IN VITRO NEUTRALIZATION, PAR. SERUM, 1:25  
Reactions at Normal Sites and their Retests

Immediate Reactions			2nd Test, 2000 u. p. c.c.		Reciprocal Test, 1000 u. p. c.c.		
Antigens	w	e	w	e	Antigens	w	c
Sagebrush	12	15	6	0	Common mugwort	6	0
Sagebrush	10	12	6	0	Silvery wormwood	6	0
Sagebrush	11	20	8	0	Calif. mugwort	7	0
Sagebrush	11	22	8	0	Green sage	7	0
Sagebrush	11	15	10	0	Coast sagebrush	5	0
Sagebrush	11	17	8	0	Pasture sage	6	0

Table II. Reactions obtained at unsensitized sites in the skin of a normal recipient, when injected intracutaneously with 0.05 c.c. of mixtures in equal parts of Par. serum, 1:25 + pollen extracts, 1,000 units per c.c. followed by 0.01 c.c. of the same pollen at 2,000 units per c.c., and their reciprocal tests with pollen extracts at 1,000 units per c.c. For explanation see Table I.

will be seen that all of the artemisiae gave reactions, though some more than others. The next day the sites were reinjected with the same antigens at double the concentration. Only two of them, common mugwort and coast sagebrush, gave even borderline reactions on the second tests, showing that the first reactions had nearly or completely desensitized the sites for the allergens used. Any residual sensitizations could certainly be counted upon to be sufficiently neutralized by the second test. The sites were then all tested with sagebrush extract, also a number of the genus *Artemisia*. Every site was found to be completely negative to sagebrush.

This is the method of *in vivo* desensitization. Since the sites are sensitized first, then tested, it has the advantage of discovering which antigens will elicit reactions, and gives a rough idea of the degrees of the specific activities of the serum. When these are known, the experiment can as well be done by combining the antigen with the serum and preparing sites by injecting the combination. This is known as *in vitro* neutralization. It has the advantage of requiring one less injection and gives essentially the same results, but the immediate reactions are unreliable, so the use of the method is restricted to allergens to which the reactions of the serum under consideration are already known.

Returning to the Par. serum, the reverse of the preceding experiment was tried. Since it was already known that sagebrush elicited reactions with this serum comparable with the most active of the other members of the genus, the *in vitro* method was used. Sagebrush extract was combined with the serum in a proportion which it was believed would completely neutralize it, and six sites were prepared by injecting the combination. Twenty-four hours later the sites were reinjected with double the concentration of sagebrush (Table II). No reactions were obtained, showing that neutralization had been complete. The sites were next tested with each of the six other members of the group. None caused reactions, showing that with this serum sagebrush is capable of neutralizing its sensitivity to at least these six other members of its genus. And since the reverse is also true, it is reciprocally neutralizing with them as if antigenically identical.

When other sensitizations of this serum were tested in the same way (Fig. 1) it was found that bur ragweed and western ragweed only partially neutralized their sites against sagebrush. Tall, short and slender ragweeds had no appreciable effect on their sites against sagebrush. But sagebrush neutralized its sites to all of these. When these latter extracts were tested against each other they proved to be reciprocally

cally neutralizing. Even bur ragweed and western ragweed, both of which could partially neutralize the sagebrush sensitization, were reciprocal with short and slender ragweed, which had no neutralizing effect on it.

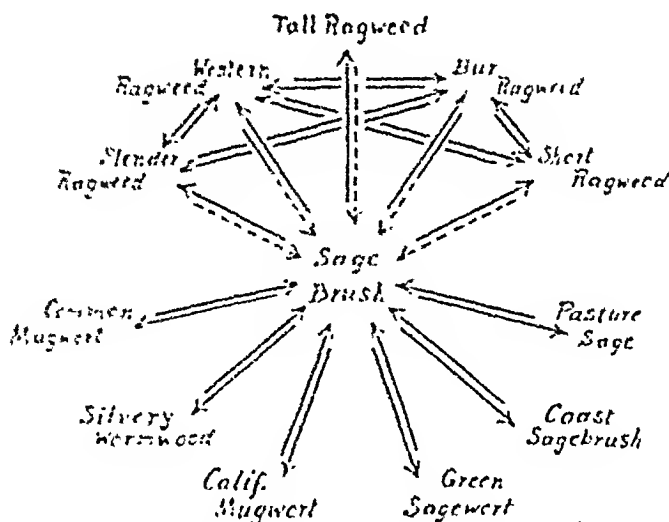


FIG. 1. Diagram of cross reactions, Pat. serum. The direction of the arrows indicates the sequence of the tests. The unbroken line indicates that the first test neutralized against the second completely; the broken line indicates no appreciable reduction in the second test; and the partly solid and partly broken line indicates that the first test materially reduced the reaction of the second but was never able to completely obliterate it.

In this serum, sagebrush is in the major position but it is reciprocal with all the other members of its genus (lower half of the diagram). It neutralizes its sites in all other sensitizations (upper half of the diagram) but none of these is able to neutralize its site against sagebrush. Only bur ragweed and western ragweed can partly do it, and these, in turn, are reciprocal with each other and with slender and short ragweeds.

This shows that the major antigen of sagebrush is identical with those of the other species of *Artemisia*, and that sagebrush contains an antigen common to the ragweeds which is not their major antigen.

Russian thistle, summer cypress and perennial ryegrass gave only borderline reactions, and cat dander, timothy, June grass, Bermuda grass and California black walnut, to all of which the patient reacted by direct test, failed to transfer with the serum concentration used.

This is a simple form of multiple sensitization. The patient's major sensitization is to the major antigen of sagebrush, and this is shared by all the species of *Artemisia*. Sagebrush also contains a minor antigen which is common to the members of the ragweed group.

**Case 2.**—Gip. was a Santa Fé stationery engineer at Prescott, Arizona, a region characterized by cedars, sagebrush, Russian thistle and western ragweed. He gave a history of severe hay fever since 1931, starting as early as January or February and lasting at first until May, virtually coinciding in extent of time with the pollination of the several species of juniper and cypress in northern Arizona. However, year by year, his symptoms became worse and lasted longer, eventually developing into asthma and reaching the end of summer. Clearly he was becoming clinically more sensitive and affected by more pollens.

At the time when his serum was obtained (1944), his case was recognized as  
JULY-AUGUST, 1948

# PATTERNS OF ALLERGIC SENSITIZATION—WODEHOUSE TABLE III. IN VIVO NEUTRALIZATION, GIP. SERUM Reactions at Sensitized Sites

Antigens	1st Test, 1000 units per c.c.		2nd Test, 2000 u. p. c.c.		Reciprocals, 1000 units p. c.c.		
	w	e	w	e	Antigens	w	o
Carelessweed	8	35	6	0	Mountain cedar	10	40
Summer cypress	8	35	6	0	Mountain cedar	10	40
Bermuda grass	6	20	6	0	Mountain cedar	8	45
Timothy	5	0	5	0	Mountain cedar	8	30
Sagebrush	9	25	6	12	Carelessweed	6	0
Mountain cedar	9	40	5	0	Summer cypress	7	0
Mountain cedar	10	45	7	0	Bermuda grass	5	0
Mountain cedar	11	40	7	0	Sagebrush	6	0
Mountain cedar	11	40					

Table III. For explanation see Tables I and II.

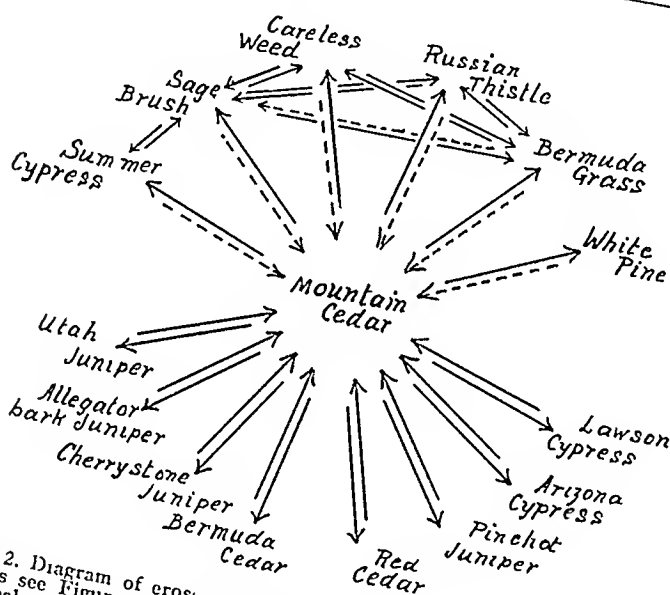


Fig. 2. Diagram of cross reactions of Gip. serum. For explanation of signs see Figure 1. Mountain cedar is in the major position but reciprocal with all members of its own genus, Juniperus, and the related Chamaecyparis (lower half of diagram). This shows that mountain cedar has a major antigen common to its group and minor antigens common to six unrelated pollens.

primarily due to the cedar pollens. By direct test he gave unusual reactions rated at 4+ to the pollen of the four species of cedar with which he was tested. He also reacted strongly to Bermuda grass, sagebrush, Russian thistle, carelessweed, summer cypress, and other later-flowering plants. He was being treated with a combination of extracts, including the principal representatives of all the taxonomic groups, and had secured considerable clinical improvement. These were tested with His serum was used to sensitize sites on normal recipients. By cross neutralization tests all were found to be reciprocally neutralizing with mountain cedar, just as the members of seven species of juniper and two of cypress. After they were desensitized by these, they remained fully active to mountain cedar. On the other hand, if they were first desensitized by mountain cedar, they proved to be insensitive to carelessweed, summer cypress, Bermuda grass and sagebrush. Cross neutralization tests with these showed that they were not all completely reciprocal (Fig. 2), as were the

## PATTERNS OF ALLERGIC SENSITIZATION—WODEHOUSE

members of the ragweed group with Par. serum. In this case Bermuda grass failed to neutralize the sites against sagebrush.

Clearly the major sensitization of Gip. serum is to the major antigen of mountain cedar, and this is identical with that of the other junipers and

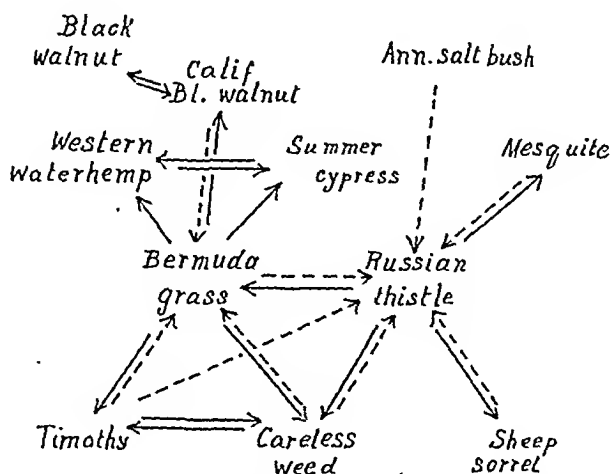


Fig. 3. Diagram of cross reactions of Ra. serum. For explanation of signs see Figure 1. Russian thistle is the major sensitization and is not reciprocal with anything.

cypress. Taxonomically these represent two genera (*Juniperus* and *Chamaecyparis*) of the Cupressinae, which is one of the six tribes of the Coniferae. Mountain cedar also has minor antigens which are common to summer cypress, carelessweed, Russian thistle, Bermuda grass, and these are not their major antigens nor are they all the same.

The Gip. serum was also tested with the pollens of related conifers, white pine, Douglas fir and hemlock of the tribe Abietinae, redwood of the Taxodinae, and yew of the Taxineae. It reacted only to the pollen of pine. However, neutralization by pine left the sensitization unimpaired to mountain cedar, while neutralization by cedar completely neutralized the pine sensation putting it in the same category as sagebrush, Russian thistle or Bermuda grass (Fig. 2). Thus it is seen that the specific antigen of the Cupressinae which corresponds to Gip.'s major sensitization, is not found in less closely related members of the Coniferae, as far as these were tested.

Since this patient's hay fever extended throughout most of the summer season, long past the pollinating period of the junipers and cypress, he owed the greater part of his clinical symptoms to minor antigens which are common to mountain cedar and unrelated species.

*Case 3.*—Ra., a resident of Los Angeles, had hay fever most of the summer. By direct test he reacted to almost every allergen tried, including sixteen species of grass, the ragweeds, amaranths and chenopods. It was concluded from his history and tests that his hay fever was primarily due to grasses. When his serum was obtained, he was being treated with extracts of seven species of grass and a heterogeneous mixture of other things in an attempt to cover all his sensitizations.

Since Bermuda grass was the most important plant flowering during the time when the patient had his worst symptoms, it seemed most likely to be the major cause of his allergy. It was put to the test (Fig. 3). This pollen neutralized some of his most important sensitizations, summer cypress, western waterhemp, California black walnut, timothy and carelessweed, but it failed to neutralize his Russian thistle sensitization. Russian thistle, however, neutralized his Bermuda sensitization. Hence, with this serum Russian thistle sensitization is predominant over that of Bermuda grass. Russian thistle was then tested against the remaining important sensitizations, sheep sorrel, mesquite and annual saltbush, and found to predominate over them. Hence, Russian thistle is Ra.'s over-all major sensitization. This pollen is not reciprocal with carelessweed nor any of the other members of the Chenopod-Amaranth group with which it was tested.

This case is of particular interest because a large proportion of the patient's clinical symptoms came from the minor antigen or antigens common to Russian thistle and the other pollens, so much so that he was regarded as primarily a grass case. This was probably due to the fact that his exposure to the minor grasses was greater than to his major Russian thistle.

*Case 4.*—Boi. was an engineer whose work required him to travel extensively. He had lived in England and several European countries and in both the eastern and western parts of the United States, and wherever he went he had hay fever, in the United States both early and late. His serum was taken in Los Angeles in November, and he was experiencing mild symptoms then. He reacted by direct test to practically every pollen which was tried; also to animal epidermals, mold, egg and some other foods. He was recognized as a Class A grass case and a most extreme example of multiple sensitization.

When his serum was taken, he was being treated with sixteen different pollens, ten grasses, two artemisias, one ragweed, and three chenopods, as a defense against the hay fever flora of California. He expected to be sent to Northern Ireland on war work so his doctor had prepared another combination better representing the hay fever flora of that country, to take with him.

When this serum was tested by passive transfer it was found to react to twenty-one different pollens, all but three that were tested. Red cedar, Arizona cypress and Lawson cypress were negative to test, though by direct intracutaneous test the patient had given a moderate reaction to mountain cedar of this group. It did transfer. Also horse and cat dander, and egg white sensitizations failed to transfer, though by direct test the patient had reacted to them.

Neutralization tests showed that timothy neutralized its sites completely to all other pollens which were tested. And only orchard grass, perennial ryegrass and sweet vernalgrass would neutralize their sites against timothy (Table IV).<sup>\*</sup> All others, including Bermuda grass, June grass and redtop, left their sites fully reactive to timothy.

The major sensitization of Boi. serum, therefore, is to the major antigen of timothy. And since orchard grass, perennial ryegrass and sweet vernalgrass are reciprocal with it and with each other, the major antigen of timothy is also the major antigen of these. Moreover, these four grasses also

<sup>\*</sup>The material upon which this report is based is recorded in more than sixty protocols of which Table I-III are typical examples. It is felt that the reference value that these might have does not warrant their inclusion here. However, they are a part of our laboratory record where they will be available for references as long as the possibility of their need shall appear to exist.

### Retest Reactions

[illegible]

Table IV. The retest reactions of sites sensitized by *Bot. serm.* The sites were desensitized by, or the serum used to prepare them was "neutralized" by, the pollen extracts in the left hand column, neutralization proved, then tested with those in the top horizontal column. The reactions obtained are recorded in vertical columns beneath the names of the retest extracts. "+" indicates that no reaction occurred with the retest, "-" indicates that the reactivity of the site was significantly impaired, and "0" indicates that the retest by the first reaction was always significantly reduced, but never completely neutralized by the first test reaction. A convenient way to read the table is by horizontal and vertical lines. Reading the first horizontal line tells that timothy neutralized its sites to everything against which it was tested. The second line tells that timothy neutralized its sites to any grass but did so to all other pollen types of the grass family. Reading the first vertical column tells that only orchard grass, perennial ryegrass and sweet vernal grass neutralized their sites against timothy. And since timothy also neutralized its sites against these three grasses they are reciprocal with timothy. Reading the second and vertical column tells that all except oak, olive and mountain cedar neutralized their sites against Bermuda grass. And Bermuda grass is reciprocal with careless weed, Russian thistle and black walnut, but not with any grasses.

behave exactly alike in their cross reactions with other species as far as these have been tested with this serum, though slight differences are brought to light in their reactions with other sera, for example Rod. serum (Table VI), in which mountain cedar neutralizes to sweet vernalgrass but not to orchard and only partly to timothy and perennial ryegrass. Hence, these four grasses are very nearly identical in both their major and minor antigens. On the other hand, Bermuda grass, and even June grass and redtop, are antigenically different from timothy, though the latter two are less so than Bermuda grass.

The position of Bermuda grass reagin in this serum is minor to that of timothy and all the other grasses with which it was tested. While the other grasses neutralized their sites to everything to which they were tested, ex-



cept to timothy, Bermuda grass failed to neutralize its sites to any other grass. And all other grasses, including the minor redtop and June grass, neutralized their sites to Bermuda grass. Even the totally unrelated Rus-

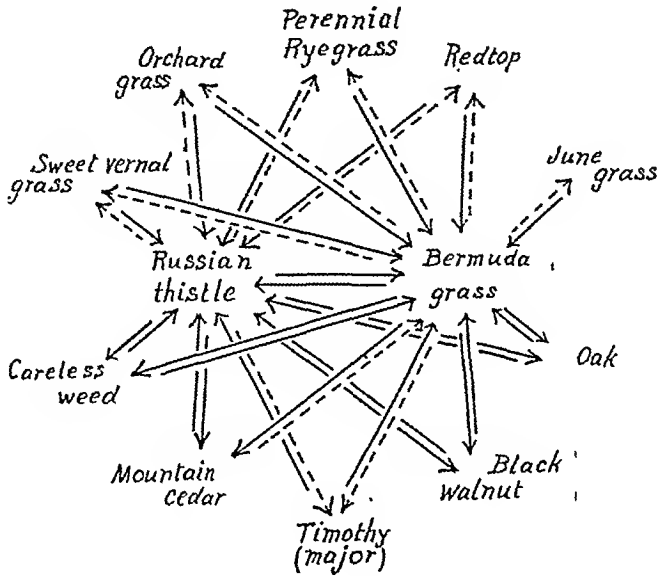


Fig. 4. Diagram showing comparison of unrelated reciprocals in the minor position with Boi. serum. They behave alike in all their relations except with mountain cedar which neutralizes Russian thistle sensitization but fails to neutralize that of Bermuda grass. For explanation of signs see Figure 1.

sian thistle carelessweeds, and black walnut do also. In other words, Bermuda grass entirely lacks the major grass antigen. On the other hand, this is probably shared by June grass and redtop which appear to lack only a specific timothy antigen since they differ only in failing to neutralize their sites to it.

Bermuda grass in this case is reciprocal with Russian thistle though entirely unrelated to it (Fig. 4). Both are reciprocal with oak and black walnut which are unrelated to either, and with carelessweed which is related to Russian thistle. They are both minor to all four grasses with which they were tested. In fact the only difference between the behavior of Bermuda grass and Russian thistle is with mountain cedar. With this pollen Russian thistle is reciprocal but the Bermuda grass sensitization is not neutralized by it. Bermuda grass behaves more like Russian thistle to which it is unrelated than it does like timothy to which it is taxonomically closely related. These reactions must, therefore, be due to the minor antigens. Bermuda grass has an antigen which is common to Russian thistle, carelessweed, black walnut and oak. It is not a major antigen because as we shall see with Rod. serum, containing the Bermuda major reagin, the Bermuda antigen neutralizes against everything but is reciprocal with nothing. The six other grasses have an antigen not in Bermuda and which is certainly the major antigen of all except possibly redtop and June grass, since the others are reciprocal with the major timothy. Russian thistle like Ber-

umbel grass, lacks the major grass antigen but has a minor antigen common to the five grasses.

With Bol. serum, Bermuda grass and black walnut are reciprocal and

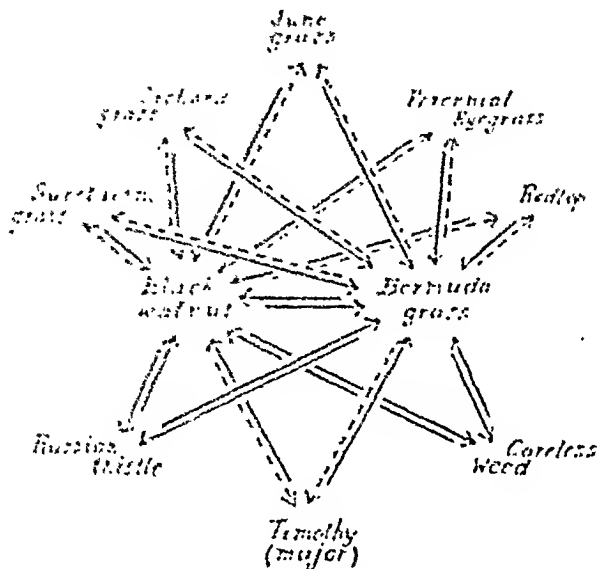


Fig. 5. Diagram of cross comparison of unrelated reciprocals, Bol. serum. They behave alike in all respects. For explanation compare with Figure 1.

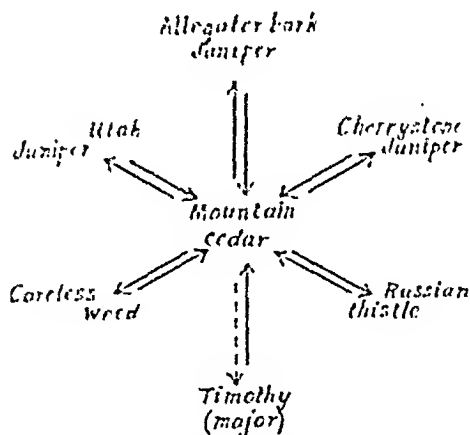


Fig. 6. Diagram of cross reactions of mountain cedar when in the minor position, Bol. serum. Mountain cedar is reciprocal with three members of its own genus, also with Russian thistle and carelessweed. Compare with Figure 2.

behave alike in all respects as far as tested. Both are reciprocal with Russian thistle and carelessweed to which they are totally unrelated, and both are minor to all the grasses (Fig. 5). Thus these two pollens also possess the same minor antigen or antigens.

The difference between the behavior of atopens towards reagins, whether

TABLE V. JAM. SERUM  
Retest reactions following neutralization

Antigens Used in Neutralization Tests	Timothy	Bermuda grass	Johnson grass	June grass	Orchard grass	Perennial ryegrass	Sweet vernalgrass	Redtop	Carelessweed	Oak	Poplar	Birch	Pecan	Elm	Willow	Short ragweed	Tall ragweed	Western ragweed	Slender ragweed	Burweed marshelder	Marshelder
Timothy		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				0
Bermuda grass	+				+																
Johnson grass	++				++																
June grass	++				++																
Orchard grass	0	±	0	0		0	0	0													
Perennial ryegrass	0				0																
Sweet vernalgrass	0				0																
Redtop	0				0																
Carelessweed	+																				
Oak	+																				
Poplar	+																				
Birch	+																				
Pecan	+																				
Elm	+																				
Willow	+																				
Short ragweed	+																0	0	0	0	
Tall ragweed	+																0				
Western ragweed																	0				
Slender ragweed																	0				
Burweed marshelder																	0				
Marshelder	+																				

Table V. The retest reactions of Jam. serum. For explanations see Table IV. The relations between timothy and Bermuda grass are similar but not identical with those in Boi. serum.

in the major or minor position, is strikingly brought out by comparing the reactions of the Cupressineae with the Gip. serum in which they were major, with those of the Boi. serum in which they are minor. With the Gip. serum, mountain cedar was reciprocal with them all but major to everything else. With the Boi. serum (Fig. 6), Red cedar, Arizona cypress and Lawson cypress sensitizations fail to transfer. Mountain cedar is found to be reciprocal with Utah juniper, alligator bark juniper and cherry-stone juniper, but more significantly, it is also reciprocal with careless-weed and Russian thistle, to both of which it is unrelated. This shows that the reciprocal neutralizations that do occur within the Cupressineae are here due to minor antigens which occur also in unrelated species.

Case 5.—Jam. was a resident of Shreveport, Louisiana, where it is believed she contracted hay fever in 1932. When her serum was taken in 1947, she was having severe hay fever from mid-February to mid-June. By direct test she had been found sensitive to all pollens tested, to dust, feathers, cat, dog and horse danders. Immunization had been attempted but never carried out on account of frequent and severe constitutional reactions.

Her serum was found to react to twenty-one different pollens (all that were tested), but the dust and epidermal sensitizations failed to transfer at the concentrations required for the pollens. Timothy was found to be the major sensitization (Table V), and as in the case of the Boi. serum it was reciprocal with orchard

# PATTERNS OF ALLERGIC SENSITIZATION—WODEHOUSE

TABLE VI. ROD. SERUM  
Retest reactions following neutralization

Antigens Used in Neutralization Tests	Bermuda grass	June grass	Perennial ryegrass	Redtop	Timothy	Orchard grass	Sweet vernalgrass	Carelessweed	Russian thistle	Summer cypress	Shadscale	Western waterhemp	Sagebrush	Short ragweed	Western ragweed	Oak	Poplar	Black walnut	Calif. black walnut	Mesquite	Mountain cedar	Sheep sorrel
Bermuda grass		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
June grass	+																					
Perennial ryegrass	+																					
Redtop	+	0	0			0	0														0	
Timothy	+	0	0	0		0	0		0	0					0						0	
Orchard grass	+			0	0				0	0											0	
Sweet vernal grass	+			0	0				0												0	
Carelessweed	+		0	0	0	0	0		0	0		+										
Russian thistle	+				+				0	0		0										
Summer cypress	+				+				0	0		0										
Shadscale	+								0	0												
Western waterhemp	+	±		+					0	0	0										0	
Sagebrush	+																					
Short ragweed	+														0							
Western ragweed					0									0								
Oak	+																					
Poplar	+																					
Black walnut																			0			
Calif. black walnut	+																	0				
Mesquite	+																					
Mountain cedar	+	±	0	0	+	0						0										
Sheep sorrel	+																					

Table VI. The retest reactions of Rod. serum. The relations of timothy and Bermuda grass are the reverse of those of Boi. and Jam. sera. Bermuda grass is the sole major sensitization. Timothy is reciprocal with June grass, orchard grass, redtop, and sweet vernal grass, but not with perennial rye grass among the grasses. On the other hand, it is reciprocal with carelessweed and western ragweed outside of the grass family.

grass, perennial ryegrass and sweet vernalgrass. But unlike the previous serum, timothy is here also reciprocal with redtop. It neutralizes against Bermuda, Johnson and June grasses but is not neutralized to test by them, except partly by June grass. Orchard grass behaves the same as timothy in relation to the other grasses except that it only partially neutralizes the Bermuda sensitization, showing that the reciprocals among the majors are almost but not quite identical.

In this serum the ragweeds are subordinate, and it is seen that tall, western and slender ragweeds and burweed marshelder are reciprocal with short ragweed. This should be compared with the pattern of the Spri. serum (*vid. ult.*) in which short ragweed is major. In the major position it is not reciprocal with slender ragweed and burweed marshelder. They do not interreact in the major position; hence, their interreaction in the minor position is through a common minor antigen.

Case 6.—Rod. was a resident of Los Angeles suffering from both early and late hay fever. By direct test she reacted to practically every pollen with which she was tested, representing all taxonomic groups, and to the animal epidermals, egg and glue. She was recognized as a case of extreme multiple sensitization and was being

treated with seven grasses and a combination of chenopods, amaranths, ragweeds and artemisias in an effort to cover as many of her sensitizations as possible.

By passive transfer her serum sensitized to twenty-two different pollens—all that were tested (Table VI). Cross neutralization tests showed that Bermuda grass

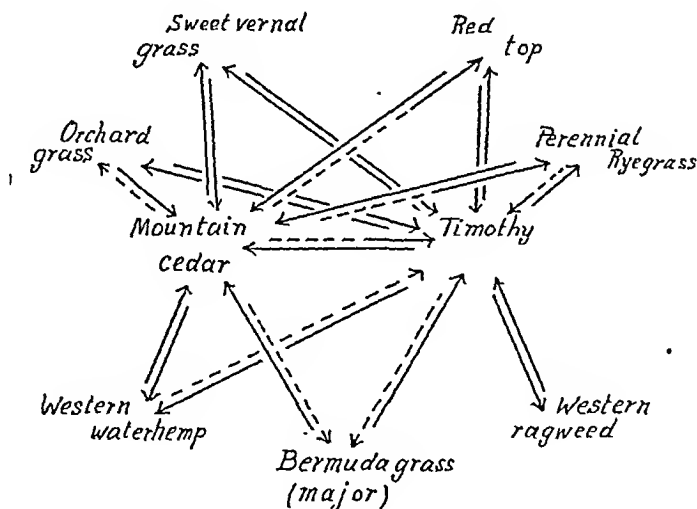


Fig. 7. Diagram showing comparison of cross reactions of unrelated half reciprocals in the minor position, Rod. serum.

neutralized its sites against all other pollens and none of them neutralized their sites against Bermuda grass. It is the sole major sensitization, finding no reciprocals among the pollens tested. The relative positions of timothy and Bermuda grass sensitizations are the reverse of what they were with the two preceding sera, and as a result timothy behaves quite differently. With this serum, timothy neutralizes its sites against all except Bermuda grass. It is reciprocal with June grass, orchard grass, redtop and sweet vernalgrass, but not with the equally related perennial ryegrass. On the other hand, it is reciprocal with the entirely unrelated carelessweed and western ragweed, showing that timothy possesses minor antigens which are common to these, though unrelated.

The wide minor-antigenic coverage of the Rod. serum reagins provided opportunity to examine the specific relations of the minor antigens. Our analysis is based on the results diagrammatically presented in Figures 7 to 9. First it is seen that the major antigen of Bermuda is lacking in carelessweed, timothy, Russian thistle and western waterhemp, because none of these desensitized to Bermuda (Table VI). Equally important is the conclusion that none of the major antigens of these four pollens is represented in the Rod. sensitization because Bermuda does desensitize to all of them. Hence, in the reciprocal tests with those four pollens, we were dealing only with minor sensitivities. This conclusion is also supported by the complete reciprocity between timothy pollen and western ragweed (Fig. 8), which again proves the absence from Rod. serum of reagins for the major antigens of these two pollens.

The mutual complete reciprocity of desensitizing property among timothy, carelessweed, orchard grass and sweet vernalgrass speaks for identity of

the minor antigens of those pollens with respect to Rod. serum. However, the further analysis is confronted by the apparent contradictions in the other reciprocal tests. Thus, carelessweed reciprocates wholly with timothy and with summer cypress; yet summer cypress seems to lack some minor

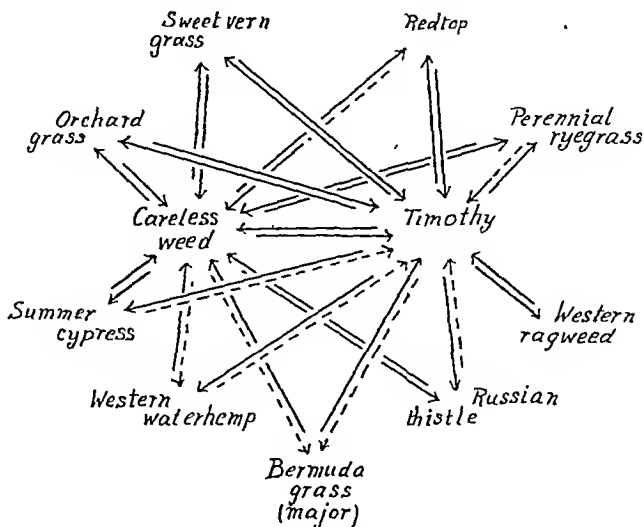


Fig. 8. Diagram showing comparison of unrelated reciprocals, in the minor position, Rod. serum. Careless weed and timothy are alike in their relations with orchard grass, sweet vernalgrass and the major Bermuda grass but differ in their other relations.

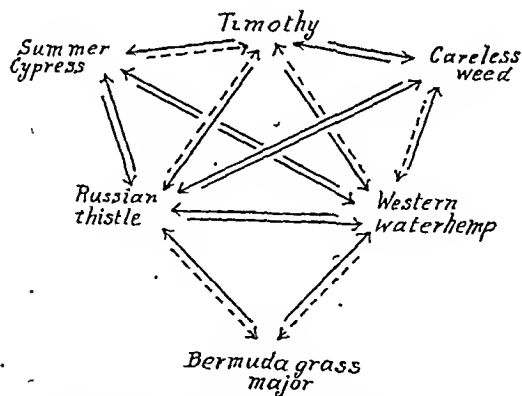


Fig. 9. Diagram showing comparison of cross reactions between related reciprocals in the subordinate position, Rod. serum.

antigen which is present in timothy. In other words, although both timothy and summer cypress equal carelessweed, they do not equal each other. This contradiction seems inexplicable purely in the terms of partial antigens; and it needs further study since other similar instances of it are seen in these studies. Thus carelessweed and western waterhemp are equal to Russian thistle but not to each other (Fig. 9); also Russian thistle and timothy are equal to carelessweed but not to each other.

# PATTERNS OF ALLERGIC SENSITIZATION—WODEHOUSE

TABLE VII. SPRI. SERUM  
Retest reactions following neutralization

Antigens Used in Neutralization Tests	Western ragweed	Short ragweed	Tall ragweed	Slender ragweed	Bur ragweed	Cocklebur	Burweed marshelder	Marshelder	Sagebrush	Plantain	Western waterhemp	Carelessweed	Russian thistle	Summer cypress	Lambsquarters	Bermuda grass	Timothy	Pecan	Ash	Oak	Birch	Elm	Mountain cedar
Western ragweed	0	0	0	0	0	0	0	0	0	0	0	0	0			0	0						0
Short ragweed	±	0	0	0	0	0	0	0	0														0
Tall ragweed	±	0	0	0	0	0	0	0	0														0
Slender ragweed	±	0	0	0	±	0	±		0														0
Bur ragweed	±	0	0	0	0	0	0		0														0
Cocklebur	±	±	±	±	±	±	±		±														0
Burweed marshelder	±	±	±	±	±	±	±		±														0
Marshelder	±	±	±	±	±	±	±		±														0
*Sagebrush	±	±	±	0	±	0	0	0		0													0
Plantain	+					0	+	+	+		0						0						0
Western waterhemp	+									0													+
Carelessweed	+																						
Russian thistle	+																						
Summer cypress	+																						
Lambsquarters	+																						
Bermuda grass	+																						
Timothy	+									0													
Pecan	+																						
Ash	+																						
Oak	+																						
Birch	+																						
Elm	+																						
Mountain cedar	+	+	+	+	+	0	+	+	0	0	0												

Table VII. The retest reactions of Spri. serum. Western, short and bur ragweeds are major and completely reciprocal. Tall and slender ragweeds fail to completely neutralize their sites to western ragweed. For further explanation see Table IV.

However, these difficulties may yield to the assumption of quantitative differences in the content of different minor antigens in the different pollens.

Case 7.—Spri. was a resident of Chicago with hay fever of the late summer type of thirty years' standing, in later years running to asthma during August. He was able to avoid attacks by spending the season in Hot Springs, N. M., but in Prescott, Arizona, he obtained no benefit from the change of climate, he believed, on account of the presence of western ragweed, bur ragweed, Russian thistle and carelessweed.

By direct test (scratch) he reacted markedly to most pollens with which he was tested, representing all the major groups, also to dust and silk. All foods were negative. By intracutaneous test he reacted to animal danders, wool, flaxseed, Kapok, orris and several molds.

His serum sensitized by passive transfer to all pollens with which it was tested, but cat, dog and horse dander, orris, feather, Kapok and house dust sensitizations failed to transfer. When cross neutralizations were tried, it was found that western ragweed neutralized its sites to all pollens tested (Table VII) but its sensitization was neutralized completely only by short and bur ragweeds, and partly by tall and slender ragweeds, and sagebrush. Neutralization of sites by all other pollens left their activity unimpaired to western ragweed.

Western ragweed sensitization is, therefore, major and it is completely reciprocal with short and bur ragweeds. These two neutralize their sites to all other pollens of the ragweed group. Hence, their major antigens are

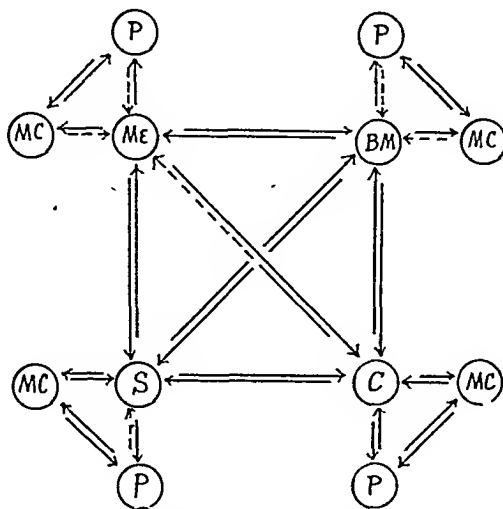


Fig. 10. Diagram showing cross reactions among some ragweed relatives with Spri. serum—marshelder, ME; burweed marshelder, BM; sagebrush, S; and cocklebur, C—and a comparison of their relations with the unrelated plantain, P, and mountain cedar, MC, showing that the ragweed relatives all contain a common minor antigen or antigens. They also all contain a minor antigen which is in plantain and one that is in mountain cedar. And mountain cedar contains an antigen which is in cocklebur and sagebrush but absent from marshelder and burweed marshelder. Plantain contains an antigen which is in cocklebur but absent from all the others.

alike but they may differ from western ragweed in their minor antigens since the short ragweed sensitization is neutralized, at least partially, by cocklebur and burweed marshelder, and bur ragweed sensitization is partly neutralized by burweed marshelder, while that of western ragweed is not. Tall ragweed only partially neutralizes its sites to western ragweed; however, it completely neutralizes them to all others of the ragweed group, and its sensitization corresponds exactly in its resistance to neutralization with that of western ragweed to all others tested. It thus appears that these four ragweeds, western, short, tall and bur, possess the same major antigen.

Sagebrush partly neutralizes the sites to the three true ragweeds and completely to all the other members of the ragweed group except bur ragweed, suggesting that it may possess the major antigen. However, its sensitization is neutralized by everything in the ragweed group and even by the unrelated mountain cedar, showing that its active antigen in this case is more probably a minor one.

Marshelder, burweed marshelder, cocklebur and sagebrush are all reacting through their minor antigens since they fail to neutralize to the major ragweeds and have their sensitizations neutralized by them. They



are all reciprocally neutralizing except that cocklebur only partially neutralizes the marshelder sensitization (Fig. 10). They are also closely related taxonomically but no more so than they are to the true ragweeds with which they are not reciprocally neutralizing. But that they are antigenically different seems to be shown by their interreactions with plantain and mountain cedar; marshelder and burweed marshelder are reciprocal with mountain cedar. They all neutralize their sites against these two pollens. But cocklebur is reciprocal with both; sagebrush is reciprocal only with mountain cedar; marshelder and burweed marshelder are reciprocal with neither. In view of the fact that plantain and mountain cedar are reciprocal with each other, this differentiation cannot at present be explained but may be due to quantitative differences.

Some significant facts emerge from these studies: Most allergic sera have a single major sensitization upon which all others depend. The homologous antigen of the major sensitization is capable of neutralizing all other sensitizations of the serum, however numerous, but the major sensitization cannot be neutralized by allergens of any but phylogenetically closely related species, presumably carrying the same major antigen. That a major sensitization among allergic sera is the rule seems certain because it was found in the seven sera reported on here, and these were selected for study only on their diversity of character, and the high degree and multiplicity of their sensitizations. Besides these, three other sera have been studied in some detail. Of one of them the major sensitization has been found to be carelessweed but of the others major sensitizations have not been found, but it has not been proved that they have none.

The major sensitization of a hay-fever patient appears to bear a definite relation to his past exposure. Thus Par. with major sensitization to sagebrush, Gip. to cedar, Rod. to Bermuda grass, and Spri. to ragweed, developed their hay fever in regions where these plants are prevalent causes of the malady. Boi., though a resident of California, where timothy and other grasses of his major sensitization are lacking, had become sensitized before taking up residence in California, either in Europe or the eastern United States, where such grasses are common causes of hay fever.

Only phylogenetically closely related species have been found to interreact reciprocally with that of the major sensitization. Thus we see the members of the genus *Artemisia* reciprocally neutralizing with sagebrush which, in turn, neutralizes unilaterally all other sensitizations of that serum. And we see the members of the genus *Juniperus* and the closely related *Chamaecyparis* reciprocally neutralizing with mountain cedar in the major position. Among the grasses reciprocal neutralizations with a major antigen do not extend throughout the whole family but only to a limited number of genera as, for example, timothy, orchard grass, perennial ryegrass, sweet vernalgrass, and more or less to redtop. The phylogenetic relationships of the grasses are not well understood. However, they are believed to be all unusually closely related for such a large family. With the exception of

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Bermuda grass the results of these studies do not violate this conception. Bermuda grass, however, stands conspicuously apart from the other grasses. When it is in the major position it finds no reciprocals among the commoner hay-fever-grasses. And when other grasses are in the major position it is entirely minor, exhibiting no serological affinity with them more than with totally unrelated species.

Minor sensitizations are those that are neutralized by the major antigen, but whose corresponding antigens fail to neutralize the major sensitization. Like the major sensitization, they depend for their origin upon environmental stimuli, but they may or may not represent clinical sensitizations of the donor of the serum. Most of them will neutralize against each other either reciprocally or unilaterally. Which will and which will not neutralize against each other is quite independent of the taxonomic relationships and even of their other serological relationships.

The most plausible explanation of these phenomena is that the antigenic complex of the pollen cell has a mosaic structure similar to that ascribed by Landsteiner to animal and bacterial cells. While it is probably susceptible of analysis in the same way that the agglutinogens of *Salmonella* and typhoid strains of bacteria have been analyzed, the present observations enable one only to say that the antigenic complex of pollen grains consists of a major antigen which is specific, and a number of minor antigens which are only partly specific. The major antigen is shared only by the pollens of very closely related species such as those of the true ragweeds, or of timothy and orchard grass. But the distribution of the minor antigens is quite fortuitous, the same antigens occurring in the pollens from all groups of plants and, if reports of other investigators are well founded, even among allergens of animal origin.

### SUMMARY

Pollen-allergic patients of the multiple sensitization type generally have a single major sensitization upon which the others all depend, no matter how numerous.

The pollen atopen has a mosaic structure similar to that of bacterial and animal cells, and is as susceptible of analysis. It consists of a major antigen which is species or group specific, being shared, if at all, only by phylogenetically closely related species; and it has a number of minor antigens which are common to related and unrelated species in an unpredictable way.

The minor antigens are capable of producing clinical symptoms.

It is a pleasure to acknowledge my indebtedness to Dr. Leon Unger, Dr. Albert Irving Clark, the late Dr. R. W. Lamson, and patients of their private practices for the sera used in these experiments.

### REFERENCES

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*(Continued on Page 392)*

## THE BEGINNINGS OF ALLERGY

### A Reminiscence

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THE allergic diseases have been known to the medical profession for hundreds of years but have been unrecognized as such until the present century. When I began the study of medicine in the last years of the nineteenth century, Dr. Osler used to tell us that asthma was a nervous reflex contraction of the bronchial musculature due to irritation of the nasal mucous membrane by odors, often aggravated by the presence of polypi in the nose. Great emphasis was laid upon neurotic antecedents and nervous personality as etiological factors.

Although a quarter of a century earlier, in 1873, C. H. Blackley<sup>4</sup> in England had demonstrated that hay fever was due to the inhalation of grass pollens, and four years later Elias J. Marsh<sup>25</sup> in New Jersey had made pollen counts and related them to the severity of his own hay fever symptoms, their work had received but scant attention. The accepted theory was that the symptoms were due to irritation of certain spots of hypersensitiveness in the mucous membrane of the nose. These were searched for and cauterized, nasal spurs were sawed off, septal deviations were crushed and polypi were removed galore. Hay fever was a lucrative source of profit to the surgically minded rhinologist. The postoperative result was usually aggravated hay fever.

Urticaria and angioneurotic edema were believed to be vasomotor manifestations of an unstable nervous system, while migraine was exclusively in the domain of the neurologist, aided and abetted by the gynecologist. Eczema was "due to acid in the blood." Ménière's disease was the property of the otologist, and epilepsy—well, the best thing to do with an epileptic was to incarcerate him in an institution and forget him. Every one of these conditions was recurrent and believed to be incurable. While attacks might be alleviated, a permanent cure was beyond the expectations of the most optimistic.

The usual success in the handling of asthma at that period is illustrated by an experience of mine while resident physician in the Lakeside Hospital in Cleveland sometime between 1903 and 1905. Dr. John Lowman had his Western Reserve students on the wards for bedside teaching. I had a case of asthma for his clinic. After discussing the symptoms he turned to one of the students and said, "Mr. Blank, why do we advise change of climate in cases of asthma?" Mr. Blank, the son of a physician, looked the professor in the eye and said, "Because you can't do a damned thing for them and hate to see them hang around your office!" Dr. Lowman

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Read before the American College of Allergists, in Atlantic City, June 6, 1947.

threw up his hands and said, "That is not what I expected, but I am afraid I will have to give you 100 per cent for that answer."

When in the fall of 1905 I began my work in London under Dr. Archibald Garrod, the leading pediatricist and medical chemist in England of his day, I took occasion to congratulate him on father's, Sir Alfred Garrad's, demonstration of the association between excess uric acid in the blood and gout. Dr. Garrod said, "It was a nice bit of work but I wish my father had never done it." On my asking why, he said, "For every gouty earl my father helped, thousands of patients with eczema, arthritis and what not have been allowed to suffer for years because both physicians and patients have been satisfied with the diagnosis 'acid in the blood.' There is excess of acid in the blood in gout and in no other disease. That diagnosis in all other conditions is the peg on which we hang the hat of our ignorance. When we discard that false tenet and begin to look for other causes of eczema and arthritis, then and only then will medicine make any advance in the control of those diseases."

During the first decade of this century, scientists were deeply interested in Theobald Smith's discovery of anaphylactic death in guinea pigs when he administered a second injection of diphtheria antitoxin. When Smith told Ehrlich of his findings, the latter had his assistant Otto<sup>31</sup> confirm and publish the results. In 1906, Roseman and Anderson<sup>35</sup> went one step further to prove that it was the horse serum, not the antitoxin element, which caused the death of the guinea pigs.

Among the other workers who devoted much time to the study of anaphylaxis in animals and to its relation to serum sickness in man were Von Pirquet and Schick<sup>47</sup> in Vienna, Paul A. Lewis<sup>23</sup> at the Rockefeller Institute in New York, and Gay and Southard<sup>11</sup> at Johns Hopkins.

When I returned from Europe in 1907 to the Rockefeller Institute, I found there my classmate and fellow medical house officer at Johns Hopkins, Dr. John Auer, working in the department of physiology under his father-in-law, Dr. Samuel Meltzer. Dr. Auer became interested in Dr. Lewis' work and, in conjunction with him, undertook an investigation of physiological aspects of anaphylaxis. With guinea pigs sensitized to horse serum, Auer and Lewis<sup>1</sup> demonstrated that anaphylactic death was due to asphyxiation, that, as the results were obtained when all nerve connections were severed, the phenomenon was the result of direct action on the bronchi, not through the central nervous system, and that anaphylactic death was due to tetanic constriction of the muscles of the walls of the bronchi, completely preventing the passage of air in or out of the lungs.

Important as were the findings of Auer and Lewis,<sup>1</sup> the epoch-making fact in connection with them was that Dr. Auer's father-in-law, in watching the guinea pigs die, was struck by the similarity between their symptoms and those of human beings suffering from bronchial asthma. When later in the year 1910 Dr. Meltzer<sup>27</sup> published his article expressing his belief

that bronchial asthma was a phenomenon of human anaphylaxis, he laid the foundation upon which has grown the science of allergy. The next year Eli Maschowitz,<sup>26</sup> in a review of anaphylaxis, grouped asthma, urticaria and eczema together and pointed out their relation to serum sickness. He also noted that all of them were accompanied by an eosinophilia.

Although Blackley<sup>4</sup> in the third quarter of the last century had scratched the skin of his arm, applied pollen thereto and obtained a wheal, the use of a scratch test was overlooked for forty years until Von Pirquet re-introduced it for the diagnosis of tuberculosis, and at the same time gave to the reaction the name of "allergy."

In 1910, Knox, Moss and Brown<sup>21</sup> at Johns Hopkins sensitized rabbits with horse serum and later injected 0.1 c.c. of a 10 per cent solution of horse serum intradermally into the skin of their ears and abdomen, and got swelling at the points of inoculation. Moss<sup>20</sup> then followed this by injecting horse serum intradermally into human beings as a test of susceptibility to serum sickness before administering antitoxin, and in a number of cases saw marked reactions.

The introduction of skin testing as a means of diagnosis, however, came with the observations of Oscar M. Schloss,<sup>38</sup> who had been a second year student when I was a house officer at Johns Hopkins. In 1912, Schloss, then teaching pediatrics at Cornell Medical College, published a preliminary report in which he cited the case of a child who had severe swellings of the mouth, tongue and lips whenever he ate eggs, oats or almonds. Using a Von Pirquet scarifier, he scratched the arm of the child and applied the offending substances. In a few minutes urticarial wheals appeared at the site of the scratches. He repeated the experiment with other foods and got negative results. He then made many experiments with the constituents of the foods and showed that it was the protein factor which gave the reaction. Clinical allergy had been born. It was, however, a sickly infant, and though receiving enthusiastic attention from its parent and a few of his friends, grew so slowly that it remained for a while quite unknown to the medical profession at large.

One friend, however, who showed great interest in Dr. Schloss' brain child was another pediatricist, Dr. Fritz Talbot<sup>43</sup> of Boston, who plunged avidly into the study of the new discovery and, in 1914, published a report<sup>57</sup> of six children suffering from asthma caused by egg who gave scratch tests to egg and were cured or greatly improved by the administration of capsules of egg albumin. In the same year J. G. Missildine<sup>25</sup> in Kansas reported two cases of horse asthma who reacted to skin tests with horse serum and were benefited by graded inoculations with horse serum. At about the same time, Goodale<sup>12,13</sup> of Boston had a series of cases of horse asthma in which he not only got reactions to diphtheria antitoxin by skin tests but also by insufflating the serum into the patient's nostrils. The next year Goodale<sup>15</sup> reported attempts to desensitize his

horse asthma cases by spraying graded doses of diphtheria antitoxin into the nose and by giving it hypodermically.

After Oskar Schloss<sup>39</sup> read his paper, "Allergy to Common Foods," before the American Pediatric Society at Lakewood, N. J., on May 24, 1915, general interest in this new addition to our medical armamentarium spread rapidly among pediatricists but more slowly among internists and otolaryngologists. In 1915, R. N. Babcock<sup>2</sup> accepted the anaphylactic theory but believed that the chief etiological factor was focal infection and advised treatment with autogenous vaccines.

In 1916, Talbot<sup>4</sup> made the next great advance when, instead of using the crude flour or juices of the foods for testing, he began applying the pure proteins of the foods, hairs, et cetera, prepared by Dr. Wodehouse, and in the same year<sup>4</sup> read before the New England Pediatric Society a paper proving that protein could pass unchanged through the intestinal wall of infants during the first few weeks of life, thus explaining a probable source of sensitization. In the same year Schloss and Werthen,<sup>40</sup> by precipitin and anaphylactic tests of the urine, showed that a similar permeability to protein was present in older infants suffering from nutritional and gastrointestinal disorders.

At about this same time, C. J. White,<sup>61</sup> in an article in the *Journal of Cutaneous Diseases*, published a paper on the relation of allergy to eczema and the value of the skin tests, apparently the first dermatologist to admit that there was more to the treatment of eczema than the application of ointments. He deplored the tardiness of dermatologists in following the pediatricist in making use of allergic methods. In the same journal, McBride and Schorer<sup>74</sup> mentioned that urticaria may be due to sensitization to certain foods but omitted any mention of skin testing. Also in 1916, Blackfan<sup>3</sup> established the relation of eczema to allergy by testing a series of children with egg, cows' and human milk, ovomucoid, barley, horse serum, and beef extract. Of forty-three cases showing no clinical evidence of allergy, all were negative; of twenty-seven having eczema, twenty-two gave positive skin tests; in all other skin diseases the tests were negative.

At about this time I began to hear rumors of the work Dr. Talbot was doing in Boston and, after attending the Tri-City Pediatric Society in that city, I remained over another day and, on the strength of Dr. Talbot's having been in the class after mine at Harvard College, I met him at the Massachusetts General Hospital. He showed me the cases he had and demonstrated the method of testing. When we returned to his office, I went into further details. He told me that at that time he had eighty different proteins with which he was testing. When asked if it was necessary to have so many, he said it was to do the work adequately. Having in mind trying the new method on two charity cases at home, I asked how expensive the proteins were. He had just received five new extracts that day, and he tossed me the bill which accompanied them. When I read

"5 protein extracts, \$300.00," I decided not to purchase eighty for two charity cases. I returned to Utica a disappointed and a wiser man and waited until the testing materials came on the market before starting on the road to becoming an allergist.

The following year Dr. Talbot came to Utica on my invitation to read a paper before the Section on Pediatrics of the Medical Society of the State of New York, of which I was chairman. While driving to my residence, Dr. Talbot remarked, "Utica! I think my father owns a store in this city, a gentlemen's furnishing store." As I looked puzzled, he said, "It is one of forty he owns in various parts of the country, none under his own name." When I suggested Wicks and Greenmans, our largest and most fashionable haberdashery, and he said, "Yes, that is it," I understood how Dr. Talbot was able to purchase eighty proteins at the rate of \$300.00 for five. When I saw him a number of years later and asked him how he was getting along with his allergy, he said, "Oh, these chaps who are doing nothing but allergy have run me out of business. I have given it up and am devoting my whole time to pediatrics." He, however, had done more to make allergy a practical science than any other man of his day.

In the meantime a number of men were studying the problem of hay fever, turning back to the work of Blackley,<sup>4</sup> ignored and neglected for forty years, until Dunbar<sup>9</sup> resuscitated it in 1903. In 1909, Scheppergell<sup>27</sup> stated that hay fever was usually due to sensitivity to ragweed and attempted to desensitize his patients by spraying ragweed pollen into the nose. Two years later Noon<sup>30</sup> in England tested patient's susceptibility to grass pollens by instilling extracts of different concentrations into the eye. He judged the patient's sensitivity by the strength of pollen solution required to produce a slight redness of the conjunctiva. He then injected pollen solutions in increasing doses. He found that, whereas if he injected the pollen every three days there was little or no increase in the patient's resistance to it, if he gave the injections at from seven to ten-day intervals the resistance increased many hundredfold. Freeman<sup>30</sup> followed up Noon's work by showing that preseasonal injections of pollen greatly lessened the severity of the attacks.

In 1915, Goodale<sup>16</sup> and also Cooke<sup>6</sup> advocated the use of skin tests for the diagnosis of hay fever, Goodale using scratch tests while Cooke recommended intradermal tests and started a controversy which has continued to the present day. Cooke and VanderVeer<sup>7</sup> the following year showed that the ability to become sensitized was inherited. In 1916, Goodale<sup>17,18</sup> also published two papers on seasonal and perennial hay fever and advocated the theory that the chronic rhinorrheas and asthmas were usually of bacterial origin and should be treated with autogenous vaccines.

In the year 1917, as a result of a grant made by Mr. Charles F. Choat, Jr., of Boston, to the Peter Bent Brigham Hospital, for the study of

bronchial asthma, Walker<sup>44,45</sup> and Wodehouse<sup>43,47</sup> published a series of seventeen articles covering all aspects of the etiology and treatment of the disease and placed the science of allergy on a firm foundation.

From this time on, the recognition of allergy spread with ever-increasing speed, and additions to our knowledge came ever more rapidly. In 1918, Rackemann<sup>32</sup> divided asthma into extrinsic and intrinsic types. In 1919, Sutton<sup>42</sup> and Hamrah<sup>46</sup> reported cases of ragweed dermatitis, and Cooke<sup>4</sup> added drug allergy to the list. In 1920, several observers including Rackemann<sup>33</sup> and Kern<sup>20</sup> called attention to the importance of house dust, especially mattress dust, as a cause of asthma. In 1922, Shannon<sup>41</sup> reported changes of disposition due to allergy, while Ratner<sup>34</sup> and Larsen and Bell<sup>35</sup> included rabbit hair among etiological factors. In 1924, Cadham<sup>7</sup> reported three cases of asthma due to grain rusts, and in 1927, Vaughan<sup>48</sup> definitely established the allergic origin of many cases of migraine.

During the third decade of the century the interest in allergy grew by leaps and bounds. Whereas the extensive bibliography in Rowe's<sup>36</sup> textbook gives but five articles on allergy written in 1914 and twenty-seven in 1920, in 1930, there were 163 and, in 1935, 317 articles on the subject. In 1923, the American Association for the Study of Allergy, with Dr. Grant Selfridge its president, and the Society for the Study of Asthma and Allied Conditions, under the presidency of Dr. Robert A. Cooke, were founded—two societies which remained rivals until the American College of Allergy was organized, when they combined under the name of the American Academy of Allergy. When in the autumn of 1929 the *Journal of Allergy* made its appearance with Dr. H. L. Alexander as the editor, allergy had attained the rank of a full-fledged specialty, and has been growing stronger ever since.

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## HISTAMINE DERIVATIVES WITH PROLONGED ACTION

(Continued from Page 357)

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# HISTAMINE TREATMENT OF FOREIGN PROTEIN TYPE REACTIONS

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THIS paper is being presented because it is believed that the treatment of foreign protein type reactions by histamine has not been adequately reported. The following cases are reported because of the severity of the foreign protein reaction and dramatic relief of symptoms, both subjectively and objectively, in response to histamine therapy.

Horton<sup>2</sup> has long entertained the opinion that "The common denominator of allergic diseases, and some diseases not now recorded as being allergic in nature, is an underlying problem of edema provoked by local release of histamine or a histamine-like substance. In the skin, localized edema manifests itself clinically as urticaria and angioneurotic edema." He has reported the use of histamine as a therapeutic agent with marked success in many subjects. Following Horton's work, we have used histamine in patients with severe urticaria and angioneurotic edema, some of whom have failed to respond to other forms of therapy.

Sherman<sup>3</sup> stated that "Reactions indistinguishable from serum sickness, and with the same incubation period, are one of the most common manifestations of sensitization to penicillin of both amorphous and crystalline forms." This author further pointed out that penicillin sensitization is usually manifested by mild and transitory symptoms. At least one death has been attributed to an attempt to use penicillin in a patient who had previously showed evidence of sensitization (Barksdale<sup>1</sup>). With all of this we agree, except regarding the period of incubation of penicillin reactions, which may be decidedly longer than that ordinarily seen in serum sickness. We further feel that emphasis should be placed on occasional severe and often critical manifestations which may be resistant to ordinary therapeutic agents including antihistaminic drugs.

The following cases of foreign protein reactions present an adequate history with clinical signs, including those described by von Pirquet and Schick<sup>5</sup> in their monograph on serum sickness, such as urticaria, erythema, edema, itching, conjunctival hyperemia, and fever. In addition, we have one case presenting a toxic psychosis which has been observed previously by Strakosch.<sup>4</sup>

## CASE REPORTS AND DISCUSSION

*Case 1.*—M. K., a thirty-one-year-old physician, entered the hospital at 10:00 a.m., May 12, 1947, complaining of urticaria, rash, edema and severe itching of two days' duration. Eight days prior to the onset of symptoms he had received oral penicillin for a urinary tract infection. The only other history of allergy was a mild attack of urticaria ten weeks previously, following an injection of penicillin in oil, for laryngitis.

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The patient was acutely ill and mentally confused. He appeared to be having a hard chill, and required several blankets. The oral temperature was 103.4° F. His skin was covered with typical urticarial wheals, and there was a generalized erythematous rash. There was marked swelling of the eyelids, and the whole face showed moderate swelling. The hands, feet and penis were markedly edematous. The conjunctivae were injected.

Intravenous histamine was started promptly on admission and gave immediate flush and relief of the chill, and many of the urticarial wheals disappeared. The patient went to sleep even though he remained disoriented. Pyribenzamine, which patient had taken of his own accord since his illness began, was continued in dosage of 50 mg. every three hours since the first hospital day without apparent results; epinephrine likewise was found to be ineffective.

During the next thirty hours he received four infusions of histamine; during this time he was definitely more comfortable and better oriented only during and for a few hours after the treatments. Furthermore, diuresis was definitely increased following the histamine, and it seemed that when an infusion coincided with a period of elevated temperature, the latter promptly subsided, although a precise relationship could not be found, since a spiking type of temperature may have been a part of the clinical picture anyway. In the hope, therefore, that if the histamine flush could be maintained constantly, more enduring improvement could be attained, a constant intravenous drip of histamine was begun at 10 p.m. on May 13. This gave continuous relief of symptoms and allowed the patient to sleep. On May 14 the edema had greatly subsided and the temperature remained normal for the first time. Except for occasional interruptions caused by the needle coming out of the vein, et cetera, histamine drip was continued for approximately sixty hours, and the patient remained comfortable after the infusion was discontinued. On May 16, histamine infusions were decreased to every six hours; itching occurred only three times during the night and then only for short periods; wheals appeared only once. On May 17 there was a little edema, and patient was out of bed for the first time. Histamine infusions were reduced to every twelve hours on May 18, and on May 19 the patient was discharged with no symptoms.

*Case 2.*—L. W. H., a thirty-five-year-old man, was admitted to the hospital August 26, 1947, presenting marked swelling of the right upper eyelid, generalized urticaria and edema of the face, hands, forearms, legs, back and buttocks of four days' duration. Two weeks prior to the onset of symptoms he had received three injections of penicillin in oil and wax. Aqueous penicillin eight months previously had caused no reaction.

There was no other personal or family history of allergy. Temperature on admission was 100° F. and rose to 101.4° F. the next day, after which it remained normal.

During the first two days of hospitalization, the patient received 50 per cent glucose intravenously, Benadryl, Pyribenzamine and epinephrine, with no results. On August 28, histamine acid phosphate (2.75 mg. in 250 c.c. of isotonic saline) was given every eight hours. Since this dosage did not cause appreciable flushing, the concentration of histamine was doubled on August 29. Improvement was immediate, particularly during and following the infusion, so that on August 31 the frequency of histamine administration could be reduced to every twelve hours. However, the patient seemed to develop a tolerance even to this double dose of histamine, but flush was restored after dosage was increased to three ampules (8.5 mg.) in each infusion. On September 3, 1947, he was discharged with no symptoms.

*Case 3.*—W. P. W., a fifteen-year-old white boy, was admitted to hospital October 2, 1947, for "hives" and loss of consciousness. Two years previously the patient

had received penicillin for pneumonia and developed urticaria. One week prior to the present illness, he received 300,000 units of penicillin in oil. On the sixth day he developed a generalized urticaria which did not respond to 200 mg. Pyribenzamine. The next day his urticaria was more intense and was complicated by nausea and vomiting, and he fainted one hour prior to admission. The patient was lethargic but responsive, and had a generalized urticarial rash and swelling of knee joints. The admission temperature was 100.2° F. Histamine intravenous drip therapy was started but with inadequate flushing; the second day the drug was doubled with only mild flushing. The temperature remained elevated until the last two hospital days. All symptoms had subsided on the eighth day of therapy, when he was discharged.

*Case 4.*—Mrs. E. A., a twenty-three-year-old white woman, was admitted to the hospital October 7, 1947. Penicillin one year previously had caused no allergic symptoms. Ten days prior to admission, she had received 300,000 units of penicillin in oil for chronic salpingitis. Two days prior to admission, she developed generalized pruritus and urticarial rash with edema of hands, face and feet, which did not respond to Benadryl. There was no record of previous allergic manifestations. Intravenous histamine drip was given with good flushing. On the third day of treatment the drug was decreased in time interval of administration because of subsiding symptoms. All lesions and symptoms subsided on the fourth hospital day. She was discharged on the fifth hospital day.

*Case 5.*—W. O. H., a twenty-year-old white man, was admitted to the hospital October 11, 1947, presenting generalized urticaria and painful joints. The patient had been well until October 1, 1947, when he received oral penicillin for pain in the right lower quadrant and a Neisserian urethritis. Symptoms developed the following day, including generalized urticaria, diffuse edema of face, hands and feet, and swelling and pain on motion of right knee.

After twenty-four hours of histamine therapy, all the urticaria had subsided; and there was only very slight swelling of the right knee on the third day, when he was discharged as improved.

*Case 6.*—N. S., a two and one-half-year-old girl, was admitted to the hospital December 10, 1947, presenting generalized giant urticaria and angioneurotic edema. On December 4 she had been given 300,000 units of penicillin in oil and wax, a sulfonamide mixture, aspirin, and phenobarbital for tonsillitis. Fever continued, and on December 8 she again received 300,000 units of penicillin in oil and wax, and it was again given December 9 because of a questionable culture. The patient was given a skin test dose of undiluted diphtheria antitoxin, and within fifteen minutes she developed a severe, giant urticaria. As antitoxin was thought dangerous, penicillin (25,000 units in saline every three hours) was given for the treatment of diphtheria; Pyribenzamine, epinephrine, ephedrine, and amytal were given for itching, urticaria and edema without effect. Intravenous procaine was tried one time without improvement. Because of the age of the patient, intradermal injections of histamine dihydrochloride were started immediately after hospitalization. Five hundredths of a cubic centimeter of 1:1000 dilution was selected as the optimum dose, and was given every two hours for fourteen hours with continuous vigorous flushing, and with disappearance of all symptoms at the end of this time. Within three hours after intradermal histamine had been started, the temperature of 105° F. (rectal) had dropped to normal, diuresis had been established, and the child had passed from restlessness to quiet sleep. Inasmuch as penicillin was continued without further reaction we believe the allergic reaction is an example of an immediate re-

TABLE I

Patient	Size of Dose of Histamine	Frequency of Treatment	Duration of Treatment	Duration of Symptoms Before Treatment	Incubation Period
M. K.	(a) 2.75 mg. HAP* in 250 c.c. N.S., I.V.	q. 6. h.	2 days	2 days	8 days
	(b) 16 ampules HAP each in 250 c.c. N.S.	continuous	60 hours		
	(c) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 6. h.	2 days		
	(d) same	q. 12. h.	1 day		
L.W.H.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	1 day	24 days	15 days
	(b) 5.5 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	2 days		
	(c) same	q. 12. h.	1 day		
	(d) 8.25 mg. HAP in 250 c.c. N.S., I.V.	q. 12. h.	1 day		
W.P.W.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	1 day	1 day	7 days
	(b) 5.5 mg. HAP in 250 c.c. N.S., I.V.	q. 6. h.	1 day		
	(c) same	q. 8. h.	1 day		
	(d) same	q. 12. h.	5 days		
Mrs. E.A.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	2 days	2 days	10 days
	(b) same	q. 12. h.	3 days		
W.O.H.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 6. h.	3 days	9 days	1 day
N.S.	(a) HAP 2.75 mg./5 c.c. 0.1 c.c. I.D.	q. 1. h.	4 hours	24 hours	immediate
	(b) Histamine 1/1000 0.05 c.c. I.D.	q. 2. h.	14 hours		
H.S.T.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	2 infusions	27 days	immediate
	(b) 6 ampules HAP each in 250 c.c. water	continuous	8 hours, could not be repeated because of edema.		
	(c) HAP 2.75 mg./c.c.				
	0.1 c.c. I.D.	q. ½. h.	4 hours		
	0.5 c.c. I.D.	q. ½. h.	1½ hours		
	0.7 c.c. I.D.	q. 1. h.	3 hours		
W.E.K.	(d) Histamine 1/100 0.1 c.c. I.D.	q. 2. h.	2 days		8 days
	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 6. h.	2 days	2 days	
	(b) 5.5 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	1 day		
	(c) HAP 2.75 mg./c.c. 0.2 c.c. I.D.	q. 2. h. q. 2. h.	1 day 1 day		
H.O'R.	(a) 2.75 mg. HAP in 250 c.c. N.S., I.V.	q. 8. h.	3 days	3 days	11 days
	(b) Histamine 1/1000				
	0.2 c.c. I.D.	q. 2. h.	2nd day) †		
	0.3 c.c. I.D.	q. 2. h.	3rd day)		
	0.4 c.c. I.D.	q. 2. h.	1 day		

\*HAP — Histamine acid phosphate

† Given in conjunction with I.V. therapy on 2nd and 3rd day.

action to a diphtheria antitoxin dose, manifested by severe edema and urticaria. Because of the age of the child it was not thought advisable to attempt intravenous administration.

*Case 7.*—H. S. T. was admitted to the hospital January 21, 1948, complaining of intense itching, redness and edema of the entire body. Oral penicillin one year previously had given no ill effect. He had received oral penicillin, two tablets, for a sore throat on December 26, 1947, and within a few minutes began to itch and soon developed a generalized edema and swelling of the tongue. Epinephrine and Bena-

dryl were given with decreasing relief. Three days prior to admission he developed generalized edema and oliguria. During this time he substituted Pyribenzamine for Benadryl without benefit. Previous allergy to sulfonamides was manifested by generalized edema in 1936.

The patient appeared critically ill, with generalized urticaria and edema; a few dry, crackling râles were heard around an old thoracotomy scar on the right thorax. Intravenous histamine was started immediately and repeated in eight hours with moderate flushing; in view of extensive edema distilled water instead of sodium chloride was used as a vehicle. The patient obtained relief of symptoms while receiving the infusion and for two hours afterwards. After twelve hours constant infusion was started and was continued for eight hours, during which time six ampules of histamine were administered, relief being noted only while the infusion was being given. By this time edema had progressed so that veins could no longer be found, and intravenous infusions had to be discontinued. In view of this, the intradermal route seemed to offer the only route of administering the drug. At first 0.1 c.c. of 2.75 mg. histamine acid phosphate per c.c. was given every half hour for four hours; only a slight flush was obtained, with little relief of itching. The amount of drug was then raised to 0.5 c.c. every half hour for three doses with little increase in flushing. Dosage was then raised to 0.75 c.c. every hour for three hours; the flush obtained lasted only about one-half hour. Histamine dihydrochloride (1:100) was then substituted, 0.1 c.c. being given every two hours for two days, with the result that a continuous flush was maintained. In spite of free fluids by mouth as well as the infusions, the urinary output was nil for the first twenty-four hours in the hospital, and was only 480 c.c. on the second day, with marked increase of generalized edema. As soon as adequate flushing was obtained, diuresis was prompt, and the urticaria and edema began to subside.

We believe that after an adequate technique for intradermal histamine administration was established in this case, the results were much more spectacular than from the intravenous route. Certainly the intradermal method afforded therapeutic action of the drug without the risk of continuing intravenous fluid in presence of the increasing edema. The patient was discharged as recovered on January 26.

*Case 8.*—W. E. K., a thirty-nine-year-old man, was admitted to the hospital January 26, 1948, for an appendectomy. A gangrenous appendix was removed, and penicillin crystals were put in the wound at the time of the operation. Seven days after the appendectomy, a hemorrhoidectomy and fistulectomy were performed. The following day, the patient developed a severe, generalized, giant urticaria with angioneurotic edema of the face and extremities and intense itching with rise in temperature to 101.8° F. He had no other allergies; however, one month previously he had received eighteen tablets of penicillin (50,000 units each) for a chest cold. The patient was treated for two days with epinephrine. Pyribenzamine, Benadryl and intravenous 50 per cent glucose, with no effect except aggravating the symptoms. On February 5, histamine infusions were started, producing a good flush with relief of symptoms during the infusion and for thirty minutes thereafter. This patient received intravenous histamine every eight hours for three days with good results. At the end of this period, intradermal therapy was substituted because intravenous injections were objectionable to him. A continuous flush was maintained on 0.2 c.c. of 2.75 mg. per c.c. of histamine acid phosphate intradermally. A clinical cure was obtained.

*Case 9.*—H. O. R., a forty-year-old man, entered the hospital February 11, 1948, complaining of "hives," severe itching and edema. A generalized giant urticaria, with some wheals ten inches in diameter, was present. There was massive edema of

face, extremities, buttocks, both knees and wrists. Two years previously, aqueous penicillin had caused a slight rash which was controlled with epinephrine. Two weeks prior to this admission, he had received three daily injections of penicillin in oil and wax (300,000 units) for a "chest cold." Eleven days later he developed his present symptoms. Pyribenzamine, 50 mg. every four hours for two days, had given no relief, but seemed to aggravate the discomfort. Temperature on admission was 99.8° F., rose to 102° F. for the next two days, and then returned to normal.

On admission 2.75 mg. histamine acid phosphate in 250 c.c. isotonic saline was administered intravenously and was repeated for three days. On the third day it was decided to supplement the infusion with intradermal therapy every two hours of 1:1000 histamine dihydrochloride, starting with 0.2 c.c. On February 14, intravenous infusions were discontinued and the intradermal injections were increased to 0.4 c.c. every two hours. The patient was comfortable as long as he was flushed, but only slight objective improvement was noted. On the fourth day, some urticaria and edema of the right hand and ankle persisted. On his last hospital day he showed no urticarial lesions and minimum edema of ankles. The patient was discharged as improved but with slight residual ankle edema on February 15.

#### METHOD OF ADMINISTRATION

Intravenous administration of histamine is the method of choice, in that the dosage can be controlled, and undue side effects can be terminated upon discontinuing the therapy. Dosage of 2.75 mg. histamine acid phosphate in 250 c.c. isotonic saline or 5 per cent glucose in water is given for the first infusion to determine the sensitivity of the patient. The rate of the infusion is regulated to a speed sufficient to just produce a generalized flush; if given too rapidly, a severe headache and substernal pain are encountered.

At first, we followed the technique advocated by Horton,<sup>2</sup> giving the infusions twice daily; but we soon found improvement was not uniformly sustained in the interval between infusions. Consequently, we have tried various intervals. We believe that the average patient does better with injections up to every six or eight hours. In our one case of extreme severity, continuous administration was necessary. When signs have disappeared, or are minimal, the infusions may be reduced to every twelve hours and eventually every twenty-four hours.

When rapid administration of the above dosage does not produce a generalized flush of the skin, the histamine acid phosphate may be increased to 5.5 mg. in 250 c.c. of vehicle.

Intradermal administration has been used when veins were obscured by edema, or in the presence of small veins, and when intravenous therapy did not give a maintained flush, and in children. This method has to be tried with caution as therapy cannot be discontinued at will. Small intradermal injections, ranging from 0.1 c.c. of histamine acid phosphate, 2.75 mg. per 5 c.c., to 0.75 c.c. histamine acid phosphate per 1 c.c. have been given. When larger quantities are required, histamine dihydrochloride 1/100 has been given in injections of 0.05 c.c. to 0.1 c.c. The dose is determined by the body flush. The dose that will produce a flush is that sought for. The flush of each dose is maintained from one-half to two hours.



In all cases treated with histamine there has been subjective relief; in two cases relief was spectacular. Some objective relief has been obtained when adequate flushing was established. There were no ill effects noted from prolonged intravenous administration. Headaches during administration have always subsided when the infusion was discontinued.

## SUMMARY

Nine patients with severe foreign protein type reactions, most of whom have failed to respond to other forms of therapy, have been treated with intravenous or intradermal histamine. In all there was clinical improvement. No definite dose or rate of medication can be established; each patient must be treated individually.

Histamine has a definite place in the treatment of severe foreign protein type reactions.

The allergic reactions resulted from penicillin in eight cases, and from horse serum in one.

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*(Continued from Page 377)*

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# A CLINICAL EVALUATION OF A NEW ANTIHISTAMINE AGENT "TRIMETON"

## A Conjoint Study of 227 Patients

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THE clinical evaluation of any drug, although often entered into lightly, is nevertheless a most complex study. No two patients are alike. None suffers from exactly identical conditions under circumstances in any way similar. At the worst, each patient reports an entirely different version of the effects, in infinite variety. At the best, however, there is some underlying consistency which may help other physicians learn what can be expected from the use of the new medication. The data are not susceptible to mathematical analysis, except superficially and on a percentile basis.

For the purposes of this investigation, Trimeton\* was distributed to the staff physicians of The Allergy Clinic of The Boston Dispensary for use in the clinic, their private practices and the separate additional clinics of which they were either chief physicians or assistants. In all, Trimeton was used by over 300 patients. Of these, seventy could not be tabulated for statistical purposes. This group includes patients who took trips, were hospitalized for conditions as varying as appendectomies and babies, suffered intercurrent illnesses, as well as those who, having received medication for symptomatic treatment, never returned to report their progress. A few of these patients were not to be trusted for adequate reports for any medications, and others were taking so much other medicine that the exact effects could not be ascertained. The 227 who remain represent both sexes and all ages from six to seventy-two, as homogenous a population as can be chosen from private and clinic practice. Such irregularities as occur are balanced by the fact that all types of patients are represented as seen by twelve physicians in five public clinics and in private practice.

The Trimeton (prophenpyridamine) was available in tablets (25 mg.). Almost all of the patients took one-half tablet three or four times daily, although some achieved excellent relief with one-quarter tablet. A few took one whole tablet, and several, two tablets, four times daily.

Trimeton differs from other antihistaminic agents in not being a derivative of ethanolamine or ethylenediamine. The chemical characteristics, the acute and chronic toxicity studies, and the antihistaminic action of Trimeton as well as comparisons with Benadryl and Pyribenzamine, both *in vitro* and *in vivo* with mice, rats, dogs, and guinea pigs have been dwelt upon separately.<sup>1,2,3</sup>

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This study was made by the staff of The Allergy Department of The Boston Dispensary, especially Dr. I. Alan Annis, Dr. Joseph H. Kaplan, Dr. Harry Korb, Dr. Joseph P. Maher, Dr. Conrad Nobili, Dr. Paul P. Norman, Dr. Russell C. Norton, Dr. Anna J. Reinauer, Dr. Sylvia Ruby, Dr. Theodore Sannella and Dr. L. Robert Weiss.

\*Trimeton was supplied through the courtesy of the Schering Corporation, Bloomfield, N. J.

The patients studied can be classified in the following syndromes: allergic coryza, vasomotor coryza, bronchial asthma, atopic eczema, urticaria, angioneurotic edema, contact dermatitis, acute coryza, migraine, exfoliative dermatitis, radiation sickness, acne rosacea, generalized pruritus and various combinations of the above, two or three conditions sometimes being present in the same patient.

The largest group was represented by the patients with inhalant nasal allergy, usually due to pollen, but also to house dust and other inhalants, sufficiently constant in their presence to permit the use of the subject for purposes of study. Of the ninety patients, sixty-two reported excellent relief, meaning complete, or almost complete, freedom from symptoms. Nineteen demonstrated moderate, although satisfactory, relief, and nine, no relief whatsoever. In seventy patients, there were no side reactions of any type. In twelve, the side reactions were manifested as slight drowsiness. In seven, the side reactions were reported as moderate, and in one, as severe.

Of special interest is the all-or-nothing type of response, seen in this and other groups described below. In five of nine patients reporting no symptomatic effect, there were no side reactions. One who had had no relief suffered a most severe reaction, marked by nausea, swollen eyelids and urethral irritation, reacting similarly, but with additional numbness and tingling, to Benadryl, Pyribenzamine and to Decapryn. Another with no effect on his symptoms had had none from either Benadryl or Pyribenzamine. One patient with excellent results reported dizziness when Trimeton was taken on an empty stomach. Eight patients having excellent results noted slight drowsiness and one a dryness of the nasal membranes. One patient suffered from a mild, transient amnesia and another from "crankiness and irritability." In all, however, in only eight patients of the ninety was it necessary to stop the medication for its side reactions.

The second largest group were the patients diagnosed as cases of vasomotor coryza. The condition was defined as a non-infectious, non-allergenic nasal coryza, characterized by a pale, boggy mucosa and symptoms which were non-environmental and non-seasonal in nature. The skin tests were negative. Of the twenty-six patients in this group, constant in symptomatology and recalcitrant to almost all previous treatment, eleven reported excellent and seven, good relief. In eight there was no effect in doses up to one tablet four times daily. In twenty-three there were no reactions. Mild drowsiness occurred in two patients and moderate drowsiness in one.

Since these patients represent a group which uses medication locally and orally of the greatest variety and amounts, the reports are worthy of detailed description. Seven showed an all-or-nothing response with no relief and no side reactions. One of these achieved good relief with Decapryn. The subject, who reported moderate drowsiness, suffered similarly from Decapryn and Benadryl. Of those reporting moderate relief, one preferred Pyribenzamine and one Decapryn. One, who re-

ported excellent relief and no side reactions, had had no relief and severe side reactions from both Benadryl and Pyribenzamine, and another had reacted violently to Pyribenzamine. Two, who had fair relief, stated that Trimeton was equal in efficacy to Pyribenzamine.

The next largest group was represented by the patients with bronchial asthma, in all, twenty-five, with pollen or other inhalant allergy, seasonal or environmental and not associated with upper or lower respiratory tract infection. Of these, fifteen suffering from mild wheezing reported excellent relief, five, moderate and five, no relief.

Mild reactions occurred in five and moderate drowsiness in one. Of the mild reactions, one was "ringing in the ears"; one "slight dryness of the mucous membranes" (also caused by Benadryl); and one "rusty taste in mouth" (better relief and no side reactions from Luasmin capsules). One patient reported nausea on three occasions and one was drowsy. Three of the patients who reported excellent results and no side reactions, took, however, supplementary medication which, alone, did not keep them satisfactorily symptom-free.

In an additional group of eight patients suffering from bronchial asthma, associated with sinus or lung infection and marked by an absence of skin tests or ascertainable allergy, three, to our surprise, achieved excellent, and one, moderate relief. Two of the former and one of the latter required additional medication, itself not sufficient to clear symptoms. In four there was no change. In none of this group, small as it was, were there any side reactions, although two of the patients took doses of two tablets four times daily, a total of 200 mg. in twenty-four hours.

Of the total number of patients studied, twenty-two had simple urticaria; two, angioneurotic edema; three, urticaria and angioneurotic edema, and one, urticaria and contact dermatitis. Of the simple urticaria patients, fifteen reported excellent, that is, complete relief; three, moderate relief, and four, no relief whatsoever. Reactions for the entire group totalled two, one of these being mild, and one, severe. The mild reaction was drowsiness, also caused by Pyribenzamine, Benadryl, and Decapryn. The severe reaction occurred in a patient who had no relief and was demonstrated by both nausea and drowsiness. In two of the patients, the pruritus was relieved but not the wheals.

Thirteen of these twenty-two patients had had other antihistaminic agents and their reports show how difficult it is to evaluate the antihistaminic group of drugs. One patient found Trimeton better than any other antihistaminic; and in another, the Trimeton not only cleared the hives but permitted the patient to eat interdicted foods. Two patients, who had partial relief on all other antihistaminics, were completely relieved with Trimeton. One patient, however, who had no relief with Trimeton was helped by Pyribenzamine, and another, who had no relief with Trimeton, was completely relieved by Decapryn. A patient, almost completely re-

lieved with Decapryn, was completely cleared by Trimeton; one patient found Trimeton and Decapryn equally efficacious; one patient, moderately relieved with Trimeton, was completely free of urticaria with Decapryn; and another, who achieved excellent results with Trimeton with no side reactions, had severe drowsiness when using Neo-antergan.

There were two patients with angioneurotic edema, one of whom was moderately relieved and the other not relieved. Neither had side reactions. Neither was relieved by any other antihistaminic agent. On the other hand, in three patients with urticaria and angioneurotic edema, all three showed complete relief; none of the three showing side reactions. One was equally relieved with Decapryn. One patient, who suffered from contact dermatitis (poison ivy) and urticaria, showed an excellent response and no side reactions with a marked diminution of all of his pruritus.

Seven patients with atopic eczema were given Trimeton for symptomatic relief of the pruritus. In three there was excellent relief; in three there was moderate relief; and in one there was no effect. The last patient had an associated fungous condition, the pruritus being unaffected by any other agent. One of the patients with moderate relief had less pruritus when taking Pyribenzamine. None of the patients in this group showed any side reactions.

General pruritus was complained of by three patients. Of these, two achieved excellent and one, no relief. None showed side reactions. The patient who was not relieved, has shown no relief from any other medication.

One patient with acute coryza found immediate relief lasting four to six hours with no side reactions; two patients with contact dermatitis had excellent relief of their pruritus with no side reactions. One patient with acne rosacea associated with flushing and pruritus had no relief and no side reactions. Of the three patients with exfoliative dermatitis associated with pruritus, two were completely relieved with no side reactions. One was moderately relieved, although he suffered slight drowsiness. He had no relief with Pyribenzamine.

Of two patients, suffering from radiation sickness, one showed excellent relief, and the other was moderately relieved. Neither suffered side reactions. Two patients with typical migraine were completely relieved of their symptoms; one with no reaction and the other with a mild drowsiness.

There was a group of twenty-one patients, showing a mixed syndrome of hay fever and bronchial asthma. Of these, eleven reported excellent results; four, moderate results; and six, no effect. The reactions were elicited as none in seventeen, and moderate in four. Six of these patients reported that the medication was excellent for their hay fever and only partially affected their bronchial asthma. One patient was relieved of the symptoms of both syndromes on two tablets (50 mg.) four times daily. One patient, who had no effects and no reactions, was relieved by Luasmin capsules. The reactions were listed in one patient as nervousness, irritability and unsteadiness; in another, as dryness of the mouth; and a third and

fourth, as slight drowsiness. One patient took additional medication which alone was not effective, but with Trimeton gave him excellent relief with no side reactions.

There were three patients suffering from hay fever, bronchial asthma, and atopic eczema, of which the bronchial asthma was quiescent in two. All three reported excellent results with no side reactions, the third patient being relieved of the nasal, bronchial and dermatological symptoms.

Two patients presented the mixed syndrome of hay fever and urticaria. Both reported excellent results, one with no reactions and one with moderate drowsiness.

In an additional two patients, hay fever and atopic eczema were coincidentally present. In neither were there side reactions, although in one there was excellent, and in the other, moderate relief. There was one patient with bronchial asthma and urticaria, who was relieved of both syndromes, being completely symptom-free while taking the medication and showing no side reactions. The relief for the urticaria was longer lasting than for the wheezing.

In total, the 227 patients presented twenty allergic and nonallergic syndromes, alone or combined. Of these, there was complete alleviation of the presenting symptoms in 140 and moderate relief in an additional forty-eight, a total of 83 per cent. In thirty-nine there was negligible effect. Side reactions appeared as slight in twenty-one (9 per cent); moderate in fifteen (6 per cent); and severe in two (less than 1 per cent).

#### SUMMARY

In summary, Trimeton, a new antihistaminic agent, was used in the treatment of 227 patients seen in routine public and private practice. Of these, 61 per cent were completely symptom-free and an additional 22 per cent moderately comfortable. Of those with hay fever, 90 per cent were relieved; with urticaria, 81 per cent; and with mild extrinsic bronchial asthma, 80 per cent. Of the side reactions, chiefly drowsiness, which appeared in 16 per cent of the patients, in 9 per cent this permitted the continuation of the use of Trimeton, leaving only 6 per cent in whom the drug could not be continued.

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# STUDY OF A NEW HISTAMINE ANTAGONIST (2-Methyl-9-Phenyl-2, 3, 4, 9-Tetrahydro-1-Pyridindene Hydrogen Tartrate)

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A NEW ERA dawned in the treatment of allergic disorders when Fourneau and Bovet, in 1933, showed that certain phenolic ethers are effective antagonists of histamine, the pathological release of which is thought to result in allergic symptoms. Soon, other compounds, having the ethylenediamine radical, were studied and this led to the quest for better drugs of this type.

In this country, two compounds were introduced: namely, beta-dimethyl-aminoethyl benzhydryl ether hydrochloride (Benadryl) and N,N-dimethyl-N'-benzyl-N'-(alpha-pyridyl)-ethylenediamine monohydrochloride (Pyribenzamine). Feinberg,<sup>1</sup> presenting an excellent review on the experimental and therapeutic status of antihistaminic agents, commented with regard to Benadryl and Pyribenzamine that "both drugs give a high incidence of side reactions, among which sedation and drowsiness are most commonly observed." Thus, there is a place for an effective antihistaminic drug which is distinguished by a lower frequency or lesser intensity of toxic reactions. With this in mind, we have undertaken the clinical evaluation of a new compound submitted to us by Hoffmann-La Roche, Inc., originally under the designation of NU-1504, and later under the name of Thephorin.\*

The drug under consideration is 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate and has the structural formula shown in Figure 1.

A comparison with the formulas of Benadryl and Pyribenzamine, also given in Figure 1, shows that Thephorin belongs to a different class of compounds.

The pharmacology of Thephorin has been explored by Lehmann<sup>2</sup> who demonstrated that it is very potent in antagonizing important physiological effects of histamine on smooth muscle, on arterial pressure, and on capillary permeability.

## CASE MATERIAL

Thephorin was used in the treatment of 140 ambulatory patients whose complaints were either proved to be due to an allergy, or were of a presumably allergic nature. There were fifty-three males, ranging in age from two and one-half to seventy-nine years, and eighty-seven females whose ages ranged from four and one-half to seventy-one years. The types of cases included nonseasonal vasomotor rhinitis; hay fever; asthma, of the

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\*Roche brand of phenindamine.

chronic and seasonal variety; various cutaneous allergic manifestations; and miscellaneous conditions. From Table I, listing separately each of the different allergic manifestations encountered, it can be seen that the 140

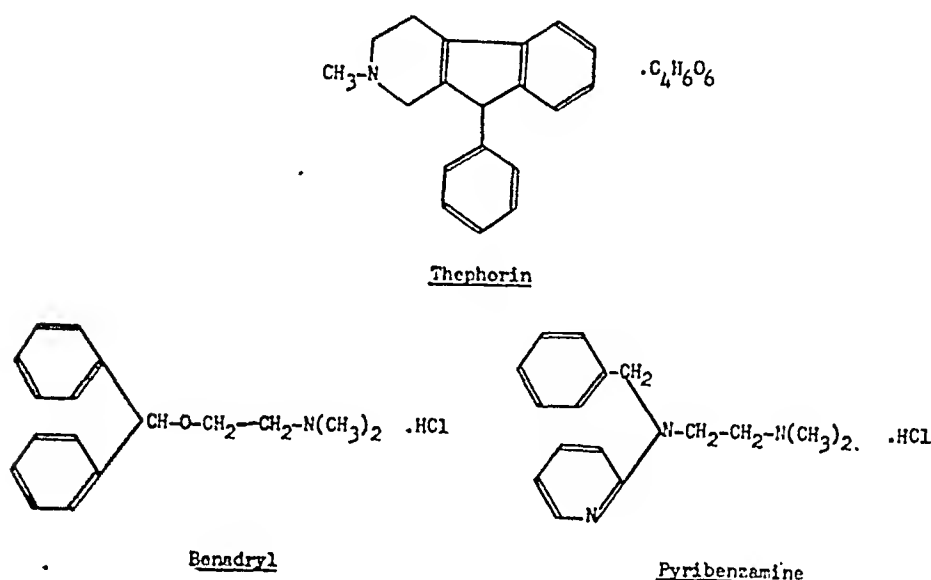


Fig. 1

TABLE I. SUMMARY OF TYPES OF ALLERGIC MANIFESTATIONS IN 140 PATIENTS TREATED WITH THEPHORIN AND OF THEIR RESPONSES

TYPES OF ALLERGY	NUMBER OF INSTANCES	NUMBER BENEFITED	NUMBER NOT BENEFITED
Nonseasonal vasomotor rhinitis	68	55	13
Hay fever	37	31	6
Asthma	31	18	13
Allergic conjunctivitis	4	1	3
Urticaria	7	6	1
Urticaria with erythema multiforme	1	1	
Angioneurotic edema	2	1	1
Neurodermatitis	5	3	2
Contact dermatitis	4	2	2
Exfoliative dermatitis	1	1	
Penicillin sensitivity	1		1
Migraine	3		3
Histamine headache	1	1	
Abdominal migraine	2	1	1
Ménière's syndrome	1		1
Aphthous stomatitis	1	1	
	169	122	47

patients showed a total of 169 allergic symptoms. In 105 instances, the patients suffered from a nasal allergy. Next in frequency were instances of asthma (thirty-one cases). The other allergic manifestations were represented by only small numbers.



## NEW HISTAMINE ANTAGONIST—FRANK

TABLE II. SUMMARY OF RESULTS AND SIDE EFFECTS IN 140 ALLERGIC PATIENTS TREATED WITH THEPHORIN

No. of Cases	Results				Total No. Improved
	Excellent	Good	Fair	Negative	
140	60(42.9%)	37(26.4%)	9(6.4%)	34(24.3%)	106(75.7%)

No. of Cases	Side Effects				
	Mild	Moderate	Severe	Total	None
140	13(9.28%)	23(16.4%)	18(12.8%)	54(38.6%)	86(61.4%)

### PROCEDURE

After a complete medical examination which, in many instances, included skin testing, Thephorin medication was instituted. The preparation was given orally in the form of 25 mg. tablets or syrup containing 10 mg. of Thephorin to the fluid dram. The syrup was used chiefly in children but occasionally also in the adult for better flexibility of dosage. Therapy was initiated with small doses: 25 mg. one to three times a day for adults, and 10 mg. at similar intervals for children. If no relief was obtained, the initial dose was increased until the patient derived benefit from the medication or until side reactions appeared. There were subjects who tolerated 400 mg. a day without untoward effects. Generally though, symptoms were controlled in adults by a total daily dose of 50 to 150 mg., and in children, depending on age, by correspondingly smaller doses. The number of treatment days ranged from one to 156 with an average of eighteen days. The maximum amount of Thephorin ingested by one patient was 6,400 mg., and this was taken in two courses of eleven and twenty-one days with a medication-free interval of twenty-five days. On an average, each patient received 1,281 mg.

If side effects occurred, medication was usually stopped; measures other than discontinuation of the drug were never required. However, frequently the patients would rather bear with an untoward reaction than forego the benefit afforded by Thephorin. In these cases, medication was continued in spite of side effects, particularly if these were of a mild nature.

### RESULTS

Thephorin gave relief to 106 patients (75.7 per cent), and thirty-four patients (24.3 per cent) were not benefited. A patient was counted as relieved if the degree of improvement derived from the drug warranted its continued use. As appears from Table II, listing the degree of the success attained and the intensity of side effects, both in relation to numbers of patients, results were excellent in almost 43 per cent of the cases studied.

*Nonseasonal Vasomotor Rhinitis*—Thephorin produced relief in fifty-five out of sixty-eight patients, an incidence of 81 per cent. Results were

excellent in thirty-three (49 per cent), and only thirteen (19 per cent) were not benefited.

*Hay Fever.*—Thephorin helped thirty-one (84 per cent) of the thirty-seven cases. Excellent relief was experienced by eighteen (49 per cent) and only six (16 per cent) were not improved.

Thus, in nonseasonal and seasonal allergic rhinitis, almost half the patients obtained excellent relief from Thephorin. Speculum examination proved objectively the shrinking of the congested nasal mucosa, sometimes within one half hour after the initial dose. It is worthy of note that two patients who for years had been completely dependent on nose drops for relief of nasal blocking, substituted Thephorin effectively for the local treatment.

*Asthma.*—Eighteen of the thirty-one asthmatic patients (58 per cent) obtained some degree of benefit from Thephorin, and thirteen (42 per cent) were not improved. Thus, the incidence of success was less than in the rhinitis cases. Moreover, the degree of relief was only moderate, with not more than six patients (19 per cent) experiencing excellent results. Generally, seasonal asthma was more amenable to treatment than chronic asthma.

*Various Other Allergic Conditions.*—All other allergic manifestations were treated in such small numbers that the percentage expression of results would be meaningless. The general trend of responses is shown in Table I.

It can be seen that three of the four patients with allergic conjunctivitis were not relieved. However, an excellent result was obtained in a nine-year-old boy who developed ophthalmic symptoms during the tree and grass season. Skin tests for pollens were negative, but eye tests were positive. The patient experienced relief within thirty minutes after the intake of Thephorin. Because of the severity of symptoms, he was given 25 mg. three times a day for two days. This dosage was then reduced to 25 mg. on a p.r.n. basis.

Of the seven cases of urticaria, six derived some degree of benefit. Thus, the further use of Thephorin in urticaria seems certainly warranted. Of the two cases of angioneurotic edema, treatment was attended by excellent results in one, and it was a complete failure in the other. Similarly, Thephorin helped three of the five cases of neurodermatitis and two of the four patients with a diagnosis of contact dermatitis. The case of exfoliative dermatitis was that of a woman, aged fifty-eight, who had been studied and treated both at the University Hospital and the Jewish Hospital. Her intractable pruritus responded well to Thephorin.

The three cases of migraine failed to derive any benefit. The one patient with a diagnosis of histamine headache was well pleased with the relief

afforded him by Thephorin. Pyribenzamine and Benadryl had succeeded also in this case. The patient now uses Thephorin during the day and Benadryl in the evening because of the concomitant sedative-hypnotic effect of the latter drug.

TABLE III.—FREQUENCY DISTRIBUTION OF SIDE REACTIONS OCCURRING IN 140 ALLERGIC PATIENTS TREATED WITH THEPHORIN

SIDE EFFECTS	OCCURRENCE IN NUMBER OF CASES
Insomnia	30
Nervousness	12
Flushes	6
Perspiration	6
Urinary symptoms	5
Palpitation and tachycardia	4
Dizziness	4
Nausea	4
Anorexia	4
Depression and drowsiness	4
Mental stimulation	3
Chilliness	3
Dryness of nose and throat	3
Headache	2
Weakness	2
Heartburn	2
Abdominal cramps	2
Decreased libido	2
Tremor	2
Chest oppression	1
Sighing respiration	1
Flatulence	1
Fever (99.6°)	1
Total	104

The patient with Ménière's syndrome remained unrelieved by Thephorin. Pyribenzamine and Benadryl had also failed to relieve this patient.

The patient exhibiting aphthous stomatitis was sensitive to tomatoes, as proved by skin testing. When placed on Thephorin, the ulcers disappeared in one or two days, whereas they lasted one or two weeks without the anti-histaminic medication.

#### SIDE EFFECTS

From Table II, it appears that side effects occurred in fifty-four persons (38.6 per cent) and that these were severe in eighteen (12.8 per cent) of the subjects treated with Thephorin. Many patients complained of more than one reaction. Thus, a total of 104 side effects occurred in the fifty-four subjects experiencing untoward symptoms. It appears from Table III, listing the various reactions in the order of their frequency distribution, that insomnia was the most commonly encountered symptom. Another not infrequent effect on the central nervous system was a state of undue excitability described by the patients as "jitteriness," restlessness or irritability, and grouped together in Table III under nervousness. Other

neurological manifestations included mental stimulation, dizziness, weakness, chilliness, diminution of libido, depression and drowsiness.

Five patients complained of urinary symptoms; viz., retention, stranguria, and frequency. There were also reactions indicating a disturbance of the gastrointestinal tract; e.g., nausea, anorexia, heartburn, flatulence, cramps; and of the cardiovascular system; e.g., palpitation, tachycardia, flushes. Untoward effects upon skin and mucous membranes were excessive perspiration and dryness of nose and throat.

It is apparent that the majority of side effects are manifestations of the central nervous stimulatory action of Thephorin. This is in contrast to the depressant effect characteristic of Benadryl and Pyribenzamine. The wakefulness after Thephorin was overcome in many instances by the concomitant administration of a mild sedative. Clinically, the stimulant action of the new histamine antagonist reminds one of the effect of sympathomimetic drugs such as ephedrine and amphetamine. However, the latter substances are chemically unrelated to Thephorin and, devoid of antihistaminic properties, act in allergic patients chiefly as vasoconstrictors. Furthermore, even the prolonged use of Thephorin has generally no effect upon the patient's pulse rate, and an effect on the blood pressure was never observed.

In keeping with the drug's stimulatory action, fatigability was lessened in many patients. In one case of allergic rhinitis, Thephorin was discontinued because the patient took the drug also as a spur against mental and physical fatigue. When the medication was stopped, after 75 mg. had been administered daily for three months, there was no craving or any other complication attributable to the withdrawal of the drug. Incidentally, urinalyses, hemograms, and electrocardiographic tracings done for this patient at initiation, during, and at termination of treatment with Thephorin, showed no significant changes.

Another subject who had derived excellent relief from his hay fever asked for a further supply of Thephorin after the pollen season because of the drug's stimulant effect. His request was denied, and he too was not unduly disturbed when the medication was discontinued. While there was thus no indication of drug addiction, this possibility, no matter how remote, must be borne in mind as with any other stimulant.

As the study progressed, the incidence of side effects decreased due to greater care exercised in individualizing the dosage plan.

In children untoward reactions occurred more rarely than in adults. In only one of sixteen patients under the age of ten years were ill effects observed. This was a six-year-old boy who, on a daily dose of 75 mg., became slightly dizzy. The reaction abated upon reduction of dosage to 30 mg. a day. However, a six-year-old girl tolerated a daily dose of 75 mg. without any untoward reactions.

## COMPARISON OF RESULTS WITH OTHER ANTIHISTAMINIC AGENTS

We have had no opportunity of rotating the patients routinely to Benadryl and Pyribenzamine after they had been treated with Thephorin. However, some of the subjects received the latter compound and one or both of the other two drugs at different times. Thus, Thephorin succeeded in five patients in whom both Benadryl and Pyribenzamine were ineffectual. Similarly, three subjects were benefited from Thephorin in whom either Benadryl or Pyribenzamine had failed. Conversely, three patients were not benefited from Thephorin, two of whom had responded satisfactorily to Pyribenzamine and one to Benadryl. Some subjects were helped by all three drugs, and others by none. However, the number of patients thus studied was too small to warrant a definite statement with regard to the comparative therapeutic value of these three histamine antagonists. It can be said, though, that, in general, smaller doses of Thephorin are required to produce salutary results than of the other two drugs.

## COMMENT

It is evident from the observations made that Thephorin is a very effective agent in combatting allergic symptoms, although it produces a high incidence of side reactions. While these are rarely severe, it is advisable to initiate therapy with a small dose (25 to 50 mg. a day in the adult) and to increase this amount according to need, once the patient's tolerance is established. Thephorin offers an important advantage in that it hardly ever produces the sedation and drowsiness so commonly observed with the other antihistaminics.

## SUMMARY AND CONCLUSIONS

A new histamine antagonist, 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate (Thephorin), was evaluated clinically in 140 allergic patients. Relief of symptoms was observed in 75 per cent. Best results were obtained in cases of nonseasonal and seasonal rhinitis. Over 80 per cent of these patients were helped, with almost 50 per cent of the total number of nasal allergies treated deriving excellent benefit. Similarly, in cases of seasonal asthma, Thephorin proved very effective. Other conditions included allergic conjunctivitis, urticaria, angioneurotic edema, neurodermatitis, contact dermatitis, and other miscellaneous allergic manifestations. The general trend of responses is discussed.

Side effects occurred in 39 per cent of the 140 subjects studied. However, even severe reactions, which were rarely encountered, required no measures other than discontinuation of the drug. The majority of side effects were manifestations of the stimulating effect of Thephorin. Insomnia may be prevented by the concomitant administration of a mild sedative-hypnotic. It is the lack of a depressant effect which distinguishes Thephorin from other antihistaminics.

*(Continued on Page 416)*

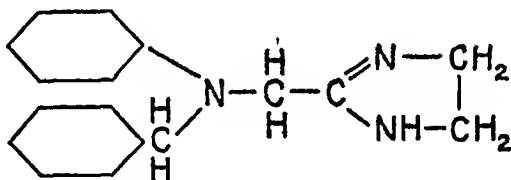
## CLINICAL EXPERIENCES WITH ANTISTINE

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SINCE the development of the Fournau and Rhone-Poulenc series of chemicals, great interest has been aroused in antihistaminic drugs. Chemists have succeeded in producing a number of such agents with varying degrees of antihistaminic activity. Needless to say, each compound put forward for clinical trial is tested for its ability to neutralize histamine *in vivo* and to prevent anaphylactic shock *in vivo*. In addition, the toxicity of each drug in clinical use must be determined, as some of these compounds possessing antihistaminic value have proven too toxic for use in humans. Recent studies summarized by Feinberg<sup>2</sup> have shown that two at least, Benadryl and Pyribenzamine, are clinically effective, but cause a high incidence of toxic side reactions.

In order to improve upon the records of the latter drugs, a new compound, 2-phenylbenzylaminomethyl-imidazoline (Antistine), was produced by Miescher in the laboratories of the Ciba Company in Basle. The product is related to Privine, 2-(naphthyl-[1']-methyl)-imidazoline hydrochloride. Its structural formula is:



Experimental work by Meier and Bucher<sup>3</sup> showed its effectiveness in the prevention of histamine effects in laboratory animals. Schindler<sup>4</sup> reported on its use in the treatment of asthma, urticaria, and pruritus. He claims that six of ten cases of asthma benefited from its use, ten of eleven cases of urticaria were helped, and nine of fifteen cases of pruritus of various etiology were helped. Bourquin<sup>1</sup> reported on its use in ophthalmology. He found response almost uniformly good in thirty-seven cases of various ocular disorders. Two patients complained of abdominal cramps and two of diarrhea. The only other side effect was pain and edema after accidental injection into the integument instead of the vein.

We have had the opportunity of using Antistine in a number of patients and feel that our results are worth reporting. A series of patients with various allergic complaints received Antistine for the control of symptoms, and the results are as follows:

*Hay Fever.*—To date, only two cases of tree pollen allergy have been treated. Both these patients were given Antistine tablets, 100 mg., as re-

quired, and obtained complete control of symptoms. Each complained particularly of conjunctivitis, and both were relieved satisfactorily by Antistine-Privine drops in the eyes. In addition to the above two cases, Antistine tablets have been used in several cases of preseasonal ragweed and grass hyposensitization for prevention and control of reactions. While such reactions have been few to date, Antistine would appear to be of value in allowing more freedom from reaction in this type of treatment. No drug reactions have been observed in these two cases.

*Asthma.*—Antistine was used in thirteen cases of asthma. Five of these are also cases of hay fever and all but two are of the extrinsic type. Five patients had good results when Antistine, 100 mg., was taken during attacks; four had some relief, not considered of much benefit, while four patients had no relief. Those who had good results had no side effects; one who had poor results had headache after taking the drug, and one had diarrhea. A young lady with severe perennial asthma, being treated by injections of autogenous vaccine, was given several injections of Antistine solution, 100 mg. each. At the site of two of the injections, considerable pain and induration developed, and a small area of necrosis eventually appeared at one site. However, she tolerated the drug orally in 50 mg. doses every three hours over a period of several weeks, without further side effects and with noticeable benefit.

*Allergic Coryza.*—Nine patients were given Antistine tablets and four were given Antistine nasal drops. These patients all had long-standing symptoms and were hypersensitive to several allergens. In only three were results noticeably good, while six did not respond. One of the latter was nauseated after taking the medication, and another had a gastrointestinal upset with cramps and diarrhea.

*Urticaria.*—Twelve cases of urticaria have been treated with Antistine, in eight of which the lesions were rapidly brought under control. One patient left off treatment, and three did not receive noticeable benefit. No side reactions occurred.

*Eczema.*—Antistine, 100 mg. every four hours, was given to five patients with severe eczema. In three cases no effect was observed. In the other two, excellent results were obtained, one patient stating that she was now able to perform many household tasks involving contact with dust, without having either eczema or asthma attacks, whereas she had formerly been assured of both if she was exposed to house dust. The other patient, who had developed conjunctivitis and blepharitis of the erythema type as a result of bacterial sensitization, was well controlled by Antistine tablets and drops in the eyes, though she experienced headaches after taking the tablets.

*Contact Dermatitis.*—Four patients were relieved of itching, and resolution of the lesions appeared to be hastened by the use of Antistine. No side effects were observed.

*Pruritus.*—Five cases of pruritus ani and one of varicose dermatitis were relieved of irritation by the use of Antistine. The drug was used in some orally; in all cases but one, a cream containing the drug in 2 per cent emulsion was also used. The pruritus associated with varicose dermatitis (one case) did not appear to benefit, while of the cases of pruritus ani treated, one patient was helped materially.

#### SUMMARY

In this report, the drug 2-phenylbenzylaminomethyl-imidazoline (Antistine) has been discussed and its use in a number of cases of allergic disorders has been described. As is the case with other antihistaminic drugs, Antistine appears to be most useful in the acute phases, and in those where the histamine mechanism is predominant in the causation of symptoms. It is less successful in chronic conditions (asthma, eczema) where other mechanisms play a greater part.

Side reactions have occurred in six of the series of forty-eight cases (12.5 per cent). Five of these reactions were related to the gastrointestinal tract, consisting chiefly of nausea, with three cases of more pronounced disturbance, including intestinal cramps and diarrhea; one headache was reported. No reaction was severe enough to require treatment other than withdrawal of medication. It is notable also that in four of the six cases with side effects, the clinical relief obtained was negligible. In the other two, reactions did not prevent the success of the treatment.

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#### REACTION: TETANUS ANTITOXIN

There is always danger that tetanus antitoxin may cause severe reactions in susceptible persons even if given in small doses for preventive purposes. Proper skin tests should be made to determine susceptibility to the antitoxin so that antitoxin can be given safely. Properly made skin tests do not cause reactions. Whether drugs can be relied on to prevent anaphylactic reaction to tetanus antitoxin is not known. (*J.A.M.A.*, Vol. 136, No. 17, p. 1118, April 24, 1948)



## TREATMENT OF ALLERGIC AND OTHER DERMATOSES WITH PYRIBENZAMINE HYDROCHLORIDE

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IN 1945, Mayer, Huttner and Scholz<sup>9</sup> synthesized a number of pyridino-ethylenediamines, the most promising of which was Pyribenzamine. Since then a number of studies have been made by Mayer and others on the antihistaminic, antianaphylactic and pharmacodynamic action of Pyribenzamine in experimental animals.

The remarkable capacity of this drug to nullify or compete with histamine in experimental sensitizations, together with its low toxicity, suggested its use in diseases in which the common denominator is the liberation of an excess of histamine.

Arbesman<sup>2</sup> and co-workers were the first to conduct clinical investigations. Their report included fifteen patients with acute urticaria, fourteen of whom were relieved with Pyribenzamine, and forty-four patients with chronic urticaria, thirty-three of whom were benefited. Three patients with cold urticaria were free from hives while taking the drug. Several patients with atopic dermatitis obtained rather decided relief from itching while taking Pyribenzamine. This group of 277 patients with various allergic disorders received from 100 to 400 mg. of Pyribenzamine daily, and only 5.4 per cent developed side effects.

Epstein<sup>6</sup> reported rapid and complete relief in eight patients with acute urticaria and symptomatic improvement in five of six cases with chronic urticaria. Pruritis was relieved in seven of nine cases of atopic dermatitis and in four of six with pruritus ani.

A summary of the literature<sup>1,3,4,7,10,11</sup> finds Pyribenzamine beneficial in the treatment of the following dermatoses: acute urticaria, 60 to 100 per cent; chronic urticaria, 60 to 83 per cent; atopic dermatitis, 9 to 100 per cent; contact dermatitis, 0 to 50 per cent; dermatographism, 85 to 100 per cent; pruritus, either localized or associated with various dermatoses, 50 to 100 per cent. There is also mention of its value in hyperidrosis, dermatitis herpetiformis and in one patient with insect bites.

The following study of the effects of Pyribenzamine on dermatoses was begun in November, 1945, when Pyribenzamine was sent to us for clinical investigation. It covers 280 patients who were observed long enough to determine the value of Pyribenzamine. The standard oral dose was 50 mg. after meals and 100 mg. at bedtime for a minimum of one week unless symptoms disappeared or side effects developed.

From the Department of Dermatology, Columbia Presbyterian Medical Center, New York, N. Y. N<sup>1</sup>-pyridyl-N<sup>1</sup>-benzyl-N-dimethylenediamine monohydrochloride (Pyribenzamine) was kindly furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J., until its acceptance by the Federal Drug Administration.

## SERUM SICKNESS

Eight patients were admitted to the overnight ward with serum sickness due to tetanus or diphtheria antitoxin injections. All presented generalized urticaria, fever and intense pruritus. In three there was edema of the face, tongue and throat, and painful, swollen joints. Since these patients were under observation, 100 to 200 mg. of Pyribenzamine was given immediately. This was followed by 50 to 100 mg. every four hours for twenty-four hours. By this time, five were free from itching. The dose was reduced to 50 mg. after meals and 100 mg. at bedtime for four to five days. Within seventy-two hours, six of the patients were cured. The two remaining patients, both of whom had swollen joints, continued the medication for a week, by which time they were also free from all symptoms.

## DERMOGRAPHISM

Four patients sought relief because of marked dermographism with pruritus. When the skin was stroked, a linear itching wheal soon appeared. Each took 50 mg. of Pyribenzamine after meals for one week. Following this, linear wheals appeared when the skin was stroked but there was no itching. Three of the patients, observed from one to five months, were free from itching and noted a diminution in the wheals on 50 mg. of Pyribenzamine after meals. The fourth patient who also had cholinergic urticaria took the standard dose for a month. At that time he was free from both symptoms. He was observed for four months, during which time there was no recurrence.

## URTICARIA

*Following Penicillin.*—Eighteen patients, while undergoing penicillin therapy for an infectious disease, developed acute generalized urticaria. In twelve it was possible to discontinue penicillin and begin Pyribenzamine therapy within forty-eight hours of the onset of urticaria. From two to five days after Pyribenzamine was instituted, eleven were free from urticaria. One of these patients with several generalized hives of four days' duration, who had been receiving massive doses of penicillin for fulminating pulmonary coccidiosis, was entirely free from hives in thirty-six hours. The twelfth patient continued to have hives after seven days of Pyribenzamine therapy. The remaining six patients took Pyribenzamine along with the penicillin. None was free from hives, but itching was less severe. In five the Pyribenzamine was continued for a week after the penicillin injections were discontinued, and all were free from hives by this time. The sixth patient discontinued Pyribenzamine because of side effects.

Six additional patients with urticaria gave a history of having had injections of penicillin one to three months previously. No other cause for urticaria was found. After one to three weeks on Pyribenzamine, four,

were free from hives. The remaining two discontinued it because of side effects.

*Cold Urticaria.*—In six patients, hives developed on exposure to cold. Three had just recovered from virus pneumonia. One patient noted that when he went out of doors in cold weather his skin began to tingle and swell. When he returned to a warm room, his face, arms and legs were quickly covered with hives, his tongue and lips became swollen and at times he had difficulty in swallowing. The attacks lasted from ten to eighteen days. On the sixth day of one of his attacks (March, 1946) he was admitted to the overnight ward. His face and tongue were markedly swollen, and his neck and upper extremities were covered with hives. He was given 150 mg. of Pyribenzamine immediately and 100 mg. after meals for twenty-four hours. The edema and itching disappeared in two hours and the wheals within twelve hours. This patient and the five others, with a similar history but less severe symptoms, were instructed to take 50 mg. of Pyribenzamine one-half hour before exposure to cold and to take an additional 50 mg. in half an hour if hives developed. During the winter months they were free from urticaria or the symptoms were minimal while varying the dose, depending on the weather and the length of exposure to it. When Pyribenzamine was not taken the symptoms recurred. In one patient, treatment could not be continued because of side effects.

*Cholinergic Urticaria.*—Three patients developed the characteristic small white hive after exposure to heat or when emotionally upset. As the provocative agents were rather unpredictable, these patients took 50 mg. of Pyribenzamine when they thought an attack imminent and again in an hour if unrelieved. Either the hives failed to appear or, if they did, itching was absent or minimal. One, a medical student, developed marked urticaria before each examination. On several occasions she has taken 50 mg. before an examination and had no urticaria. If she develops hives because of an unpredictable emotional strain, she takes 50 mg., and the hives do not itch, and disappear more rapidly than without the Pyribenzamine.

*Food Urticaria.*—Forty patients had a history of a specific food causing an attack, or subsequent study strongly suggested food as the cause. The duration was from two to twenty days. Eight patients, without any restriction in diet, were free from urticaria within three days on the standard dose of Pyribenzamine, and twelve had cleared within a week. There has been no recurrence over a period from one to eight months. One of these, a nurse, ate part of a dill pickle, and within a very short time developed swelling of the tongue and throat, difficulty in breathing and generalized hives with marked pruritus. Because of the severity of symptoms she was admitted to the hospital. Four years previously the patient had eaten a dill pickle. At that time she felt ill and had hives for a few days. The

patient received adrenaline, ephedrine and dihydroergotamine for forty-eight hours. Symptoms were unabated. The third day she was given 150 mg. of Pyribenzamine, and within two hours all symptoms had disappeared and she slept for fourteen hours. Pyribenzamine was continued for another day, a total of 350 mg., with no return of symptoms.

Fourteen patients continued to have urticaria after a week's trial of Pyribenzamine, but itching was absent or reduced. Six were not benefited. The drug was discontinued in three because of side effects.

Five patients ate the food to which they were sensitive an hour after taking 100 mg. of Pyribenzamine. Hives occurred in all, but itching was absent or minimal.

*Due to Aspirin.*—Two patients developed severe urticaria after aspirin. At one hour and at an hour and one-half, respectively, after taking 100 mg. of Pyribenzamine, they swallowed 5 grains of aspirin. One developed generalized giant hives in ten minutes and the other within thirty minutes. The patients felt that the attacks were as severe as previously, but in one the itching was less marked.

*Due to Trichinosis.*—One patient with trichinosis developed urticaria with severe itching. He received the standard dose of Pyribenzamine for one week. Itching was relieved within a few hours, and the hives disappeared in two days. On the tenth day the urticaria and itching recurred. The standard dose was again given for two weeks. The response was again prompt and there was no return of urticaria. The white blood cell count of around 5,000 with 15 to 20 per cent eosinophiles was not influenced by Pyribenzamine.

*Of Unknown Cause.*—Ninety patients, with chronic recurrent urticaria varying in duration from a few months to several years, were given the standard dose for at least two weeks unless side-effects developed. In five there was a complete disappearance of urticaria. Forty felt that the attacks of urticaria and particularly the itching were distinctly lessened while taking Pyribenzamine. One emotionally unstable patient had had recurrent giant hives for seven years. About once or twice a week it was impossible to go to work because of the marked swellings. On the standard dose she was free from attacks for two months. Then it was necessary to reduce the dose to 25 mg. twice daily because of dizziness. The patient has continued this dose for sixteen months. Mild swellings occur occasionally but are not incapacitating. Complete blood counts, done at monthly intervals, have remained normal. Thirty patients were not benefited, and fifteen discontinued the drug because of side effects.

#### ALLERGIC ECZEMA

Twenty adults with chronic recurrent eczema of the face, neck and flexures, who had been observed over a considerable period, were given

the standard dose of Pyribenzamine during an acute exacerbation. This supplemented an antiallergic regime and local medication. Twelve experienced appreciable relief from itching, were less irritable and slept better. Side effects were observed in four patients.

Twenty infants and children with generalized eczema and intractable itching were given from 10 to 30 mg. of Pyribenzamine at four-hour intervals for a few weeks. The incessant rubbing and scratching of the skin was greatly reduced in fifteen. Almost all slept from six to seven hours uninterruptedly at night with the Pyribenzamine. However, the eczema did not clear until the sensitizing allergens were removed from the diet and environment.

#### DERMATITIS VENERATA

Twenty-six patients had a dermatitis due to sensitization to substances with which they had come in contact. In ten it was due to poison ivy. These received the usual local treatment together with the standard dose of Pyribenzamine. Five who previously had had "poison ivy" felt that the outbreak and itching were less severe than previously. After the attack, two patients took the standard dose of Pyribenzamine for five days. On the third day a patch test to poison ivy (Lederle 1:5,000) was applied to the skin. A vesicular dermatitis appeared at the test site in twenty-four hours in both patients, but itching was absent.

The remaining sixteen patients had localized eruptions from one of the following substances: formaldehyde, hair dye, face powder, nail polish, nickel, zinc sulfate, mercury, nupercaine, penicillin, pyrethrum and primrose. They received the standard dose for a week. In ten the itching almost disappeared within a few days. In the remaining six, there was no change. Five discontinued the drug because of side effects.

#### PRURITUS

*Generalized.*—Five patients with intractable pruritus were given the standard dose for two weeks. Two were over eighty years of age, with wasted skin, and the remaining three were women in the latter half of pregnancy. All were relieved of itching as long as the drug was continued.

*Localized.*—Two patients with a marked pruritus of the legs from Nylon stocking were able to wear them if they took 25 to 50 mg. of Pyribenzamine three times a day.

*Lichen Simplex Chronicus (Vidal).*—Five patients with localized patches of eczema were given the standard dose of Pyribenzamine, and the areas were covered with a gauze bandage. The treatment was continued from three to four weeks. In four the itching subsided in a few days, and the patches cleared in about two weeks. In two the patches recurred after the Pyribenzamine was discontinued. One developed side effects.

*Pruritus Ani.*—Fifteen patients with marked itching of the anal area were given Pyribenzamine and an antipruritic ointment. After two to three weeks, ten were free from symptoms. A dose of 50 mg. after dinner and at bedtime was then given for another two weeks, with complete relief. The remaining five experienced little relief, and in three the drug was discontinued because of side effects.

#### OTHER ITCHING DERMATOSES

Four patients with severe erythema multiforme, in which wheals and itching were prominent symptoms, were given the standard dose for from four to fifteen days. One with a lymphosarcoma, who developed erythema multiforme after radiation, was free from itching and wheals in three days. The others noted a diminution in itching while on Pyribenzamine, but the lesions were not influenced. One with a history of dermatitis due to ragweed developed a severe dermatitis while receiving injections of ragweed antigen; another had a polymorphous generalized eruption after gold injections; two others had lichen planus of the extremities; a fifth had exudative discoid and chronic lichenoid dermatitis. All were given the standard dose of Pyribenzamine for at least a week in an attempt to allay the severe pruritus. In all the itching was suppressed or minimal and the skin less traumatized while on Pyribenzamine. Side effects developed in one patient.

#### SIDE EFFECTS

In thirty-six of the 280 patients, symptoms developed which caused them to stop Pyribenzamine. These usually occurred a few days after the drug was started. In none were the symptoms alarming, and in all they subsided shortly after the drug was discontinued. The nervous and gastrointestinal systems were most frequently affected. In order of frequency the patients expressed these symptoms as follows: feeling queer, drunk, dizzy, unsteady, nervous, hyperactive, drowsy, depressed, or developing headache, upset stomach, indigestion, dry mouth, vomiting, nausea, cramps, burning on urination, and palpitation.

#### COMMENT

The pioneer studies of Dale and Laidlaw<sup>5</sup> and of Lewis and Grant<sup>6</sup> demonstrated the similarity of allergic and anaphylactic reactions in man and animals to the effects produced by the injection of histamine.

Since then, numerous workers have attempted to inhibit these histamine effects. Recently the ethylenediamine derivatives, of which Pyribenzamine is one, have been developed. The unfolding of this research is well reviewed by Feinberg.<sup>7</sup>

Pyribenzamine is a most useful therapeutic agent in allergic symptoms which follow the administration of antitoxin or penicillin. Its continued use exerts a prophylactic action in patients with physical allergies and

dermographism. Lastly, it is most worthy of trial in a number of dermatoses in which itching is marked.

It is difficult to evaluate the efficacy of Pyribenzamine in a disease as elusive as urticaria. However, the promptness with which the urticaria disappeared in 25 per cent and was controlled in another 40 per cent while on Pyribenzamine warrants its use.

The results of Pyribenzamine therapy are summarized in Table I.

TABLE I. SUMMARY OF TREATMENT WITH PYRIBENZAMINE

Disease	Number of Patients	Results		Side-Effects
		Complete Relief	Suppressive Action	
Serum Sickness	8	6	2	0
Dermographism	4	1	3	0
Urticaria				
After penicillin	18	11	5	1
After penicillin (?)	6	4	0	2
Cold	6	0	5	1
Heat	3	0	3	0
Foods	40	20	14	3
Drugs	2	0	0	0
Parasites	1	0	1	0
Cause unknown	90	5	40	15
Allergic Eczema				
Infants	20	0	15	0
Adults	20	0	12	4
Dermatitis Venenata	26	0	15	5
Pruritus	27	0	21	4
Other Itching Dermatoses	9	0	8	1
Total	280	47	144	36

## SUMMARY

Pyribenzamine was beneficial in the treatment of approximately 68 per cent (191 of 280) patients with allergic and other itching dermatoses.

Prompt and complete relief was obtained in patients with serum sickness and in many patients with urticaria due to penicillin.

The continued use of Pyribenzamine effectively controlled physical allergies and dermographism.

Pyribenzamine completely relieved or controlled the symptoms in 65 per cent of patients with urticaria and depressed itching in approximately 60 per cent of patients with allergic eczema, in 40 per cent with dermatitis venenata and in 75 per cent with pruritus.

The antipruritic and sedative effect of an orally administered drug makes Pyribenzamine a welcome adjuvant in the treatment of a variety of dermatoses accompanied by severe itching.

Pyribenzamine was discontinued in about 13 per cent of the patients because of side effects.

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(Continued on Page 438)

# BRONCHIAL ASTHMA DUE TO INGESTION OF FENNEL AND FENNEL SEED

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**A**LLERGY to fennel and fennel seed has been unreported in the literature.

*Botanical History.*—FENNEL<sup>1</sup> (AS. *fenol*, from Lat. *fœniculum*, fennel, diminutive of *fœnum*, *fœnum*, hay), *Fœniculum*, a genus of umbelliferous plants allied to dill, and<sup>2</sup> to carrot, celery, parsley and parsnip. The flowers are yellow. All the species are aromatic and have much divided leaves with threadlike segments. The best known is common fennel, *Fœniculum vulgare*, a native of the south of Europe. It is a biennial, 3 or 4 feet tall, cultivated in many gardens in both Europe and America, chiefly for the sake of its leaves, which are used for flavoring, but also for its aromatic seeds. Florence fennel, sweet fennel, Italian fennel, or Cretan fennel (*Fœniculum dulce*) is of lower growth, much cultivated in the south of Europe. The enlarged bases of its leafstalks, after being bleached like celery, are boiled and served with drawn butter like cauliflower. The fruit (seed) is longer and paler than that of common fennel, has a more agreeable odor and flavor, is the favorite aromatic condiment of the Italians, and is used in medicine. Oil of fennel, an aromatic, stimulant, and carminative essential oil, is also made from it. Cape fennel (*Fœniculum capense*, or *Carum capense*), found in the vicinity of the Cape of Good Hope, has a thick, aromatic esculent root. The Panmuhoree of India (*Fœniculum panmorium*) is a species of fennel much cultivated in its native country for its sweet, warm, and aromatic fruit, which is much used as a carminative and in curries. The "giant fennel" of the south of Europe is a plant of a different genus (*Ferula*) and abounds in a fetid juice. It is, indeed, closely allied to asafetida. The species mentioned above, except *Fœniculum capense*, have recently been combined under the name *Fœniculum vulgare*.

## CASE REPORT

A nine-year-old boy (J. P.) of Italian descent, complaining of seasonal hay fever and asthma of two years' duration, was first seen on October 29, 1946. Family history: A paternal uncle had asthma. Past history: The patient had the usual childhood diseases, and had a tonsillectomy and adenoidectomy at five years of age because of frequent "colds."

Present illness: The patient had been well until August and September, 1945, when he developed his first seasonal hay fever. Early in November, 1945, he had a two-day attack of asthma which required adrenaline for relief. He remained well until August and September, 1946, when hay fever recurred. During October, 1946, there were many attacks of asthma, several of them severe enough to require repeated injections of epinephrine. The boy's parents stated that some of the asthmatic at-



tacks occurred within five minutes after eating fennel and sausages containing fennel seed.

Physical examination revealed a well-developed and well-nourished boy with marked dyspnea, wheeze, and cough. The chest was hyperresonant to percussion, and the lungs were filled with sibilant and sonorous râles more on expiration than inspiration. The breath sounds were distant. Epinephrine 0.3 c.c. relieved the attack, and twenty-four hours later the chest and lungs were normal.

Intradermal skin tests demonstrated positive reactions to ragweed pollen, fennel, and fennel seed. Passive transfer tests, using the father as the recipient, were positive for ragweed, fennel and fennel seed; these reactions were marked, and the reaction for the fennel test was accompanied by intense itching.

Asthmatic attacks were reproduced several times by eating fennel and sausages containing fennel seed; sausages without fennel seed did not cause asthma. The patient was placed on perennial ragweed therapy, and fennel and fennel seed were eliminated from his diet. He has been completely free of asthma since the omission of these foods.

#### SUMMARY

1. Bronchial asthma due to ingestion of fennel and fennel seed is here reported for the first time.

2. Positive skin tests with these allergens, the transfer of their reagins passively to a recipient, the reproduction of asthma after eating these foods, and the relief from asthma by their elimination from the diet, demonstrate that fennel and fennel seed may be a cause of bronchial asthma.

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- 35-16 76th Street,  
Jackson Heights, New York, N. Y.

## STUDY OF A NEW HISTAMINE ANTAGONIST

(Continued from Page 404)

The new compound provides only symptomatic relief, as do the other histamine antagonists established in therapeutics. These preparations are no substitutes for the usual procedures in the therapy of allergy, such as elimination of allergens and hyposensitization. Thephorin was found to be a valuable adjuvant to such treatment. It also proved effective in relieving allergic symptoms in a great percentage of patients not undergoing the usual procedures.

#### REFERENCES

1. Feinberg, S.M.: Histamine and antihistaminic agents, their experimental and therapeutic status. *J.A.M.A.*, 132: 702, 1946.
2. Lehmann, G.; Hagan, E.; Barbarow, G.; and Roe, M.: The antihistamine action of pyridindene derivatives. *Federation Proc.*, 6: 350, 1947.

Headquarters  
Heathman Hotel  
Portland, Oregon

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## AMERICAN COLLEGE OF ALLERGISTS FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

Under the Auspices of  
The University of Oregon Medical School  
Monday, November 8, to Friday, November 12, 1948, Inclusive  
DETAILED INFORMATION—REGISTRATION BLANK—  
SCHEDULE OF FACULTY

The regular fall, intensive, graduate continuation course in allergy will be held at the University of Oregon Medical School, Portland, Oregon, commencing Monday, November 8, and extending to Friday, November 12, inclusive.

Final registration will commence at 8:00 a.m., November 8. The daily hours of instruction will extend from 9:00 a.m. to 1:00 p.m., and from 2:00 p.m. to 5:00 p.m. Various lectures will be accompanied by graphic and clinical demonstrations, lantern slides, colored films, charts, et cetera. Printed comprehensive abstracts of lectures, with space for notes, will be placed on sheets perforated to fit a standard ring book and will be furnished to each registrant. The course includes all phases of the subject and will be presented by specialists in the fields of the basic sciences, as well as by specialists in allergy, who will deal with the treatment and management of the allergic patient. There will be two evening round-table discussions towards the end of the course.

Hotel reservation cards must be requested from the office of the Secretary, The American College of Allergists, 423 La Salle Building, Minneapolis 2, Minnesota. After the card is completed, it should be mailed directly to the Heathman Hotel. Reservations may also be made by writing directly to Mr. Harry E. Heathman, Manager, Heathman Hotel, Portland 5, Oregon. *Be sure to state the exact time desired for your reservation.* The rates for a double bedroom with bath for two per day are \$5.50, \$6.50, and \$7.50; for a twin bedroom with bath for two per day, \$6.50, \$7.00, and \$8.00; for a suite with parlor, bedroom and bath the rates per day, \$14.00, \$16.00, and \$18.00; two-room suites with bath for three persons per day, \$9.50 and for four persons, \$12.00. If a room at the rate requested is not available, reservation will be made at the next rate.

The fee for the course is \$75.00. A very limited number of scholarships are available to residents and interns interested in allergy or on an allergy service. Application for such scholarships should be made to the Office of the Secretary, 423 La Salle Building, Minneapolis 2, Minnesota, and they will then be referred to the Committee for that purpose.

Members of the College, as well as candidates for Active and Associate Fellowships and non-members, are urged to register before November 8 by mail.

.....  
Date

### REGISTRATION BLANK

To be completed and mailed to:  
Office of the Secretary  
American College of Allergists  
423 La Salle Medical Building  
Minneapolis 2, Minnesota

(Type or Print).....  
Last Name Initials

.....  
Street

City

Zone

State

Check or Money Order Enclosed ☐  
Will Remit at Time of Registration ☐  
Member ☐  
Non-Member ☐  
Candidate ☐



THE AMERICAN COLLEGE OF ALLERGISTS  
FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

UNIVERSITY OF OREGON MEDICAL SCHOOL  
PORTLAND, OREGON

November 8-12, inclusive

SCHEDULE OF SUBJECTS AND FACULTY

Monday, November 8

*Fundamentals of Allergy and Miscellaneous Manifestations*

A.M.

- 8:30- 9:30 Registration  
9:30- 9:45 Address of Welcome  
DAVID BAIRD, M.D., Dean, University of Oregon Medical School, Portland, Oregon.  
9:45-10:40 Bronchial Asthma—Diagnosis  
HARRY L. ROGERS, M.D., Jefferson Hospital Allergy Clinic, Jefferson Medical College, Philadelphia, Pennsylvania.  
10:45-11:35 Bronchial Asthma—Treatment  
HARRY L. ROGERS, M.D., Jefferson Hospital Allergy Clinic, Jefferson Medical College, Philadelphia, Pennsylvania.  
11:45-12:30 Immunological Aspects of Allergy  
HARRY SEARS, Ph.D., Professor of Bacteriology, University of Oregon Medical School, Portland, Oregon.

P. M.

- 2:00- 2:55 The Physiology of Allergy  
WILLIAM YOUNG, M.D., Professor of Physiology, University of Oregon Medical School, Portland, Oregon.  
3:00- 3:55 Pharmacology of Drugs Used in Allergy  
NORMAN A. DAVIS, M.D., Professor of Pharmacology, University of Oregon Medical School, Portland, Oregon.  
4:00- 4:25 Cardiac Asthma  
HOWARD LEWIS, M.D., Professor of Medicine, University of Oregon Medical School, Portland, Oregon.  
4:30- 5:00 Ulcerative Colitis  
ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, Berkeley, California.  
7:00 Informal Dinner  
Speaker: GEORGE E. ROCKWELL, M.D., President, The American College of Allergists.

Tuesday, November 9

*Gastrointestinal and Food Allergy*

A.M.

- 9:00- 9:40 Food Allergy  
ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, Berkeley, California.  
9:45-10:25 Migraine  
J. WARRICK THOMAS, M.D., Thomas Clinic, Richmond, Virginia  
10:30-11:10 Elimination Diet for the Diagnosis and Control of Food Allergy  
ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, Berkeley, California  
11:15-11:55 Dietary Management of Food-Sensitive Patients  
ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, Berkeley, California.  
12:00-12:30 Bacterial Allergy  
ROBERT LOUIS BENSON, M.D., Clinical Professor, University of Oregon Medical School, Portland, Oregon.

## *Clinical Allergy*

P. M.

- 2:00- 2:30 Skin Test—Demonstration  
ROY MATTERI, M.D., Clinical Instructor, University of Oregon  
Medical School, Portland, Oregon.
- 2:30- 5:00 Clinical Session (Skin Testing, Technic, and Interpretation and Demonstration of Preparation of Extracts)  
MERLE W. MOORE, M.D., Assistant Clinical Professor, University of Oregon Medical School, Portland, Oregon.

Wednesday, November 10

### *Dermatologic Allergy*

A.M.

- 9:00-10:35 Allergic Dermatoses—Atopic and Contact Dermatitis  
A. ROSTENBERG, JR., M.D., Associate Professor of Dermatology, University of Illinois College of Medicine, Chicago, Illinois.
- 10:40-11:10 Urticaria and Angioneurotic Edema  
MERLE W. MOORE, M.D., Assistant Clinical Professor, University of Oregon Medical School, Portland, Oregon.
- 11:15-11:45 Drug Allergy  
GEORGE E. ROCKWELL, M.D., President, The American College of Allergists, Milford, Ohio.
- 11:50-12:50 General Principles of Cutaneous Allergy Therapy, Including Emergency Skin Manifestations  
A. ROSTENBERG, JR., M.D., Associate Professor of Dermatology, University of Illinois College of Medicine, Chicago, Illinois.

### *Pediatric Allergy*

P. M.

- 2:00- 2:40 Infantile Eczema  
M. MURRAY PESHKIN, M.D., Instructor, College of Physicians and Surgeons, Postgraduate Medical Extension, Columbia University, New York, New York.
- 2:45- 3:25 Management of the Pre-Allergic Child  
M. MURRAY PESHKIN, M.D., Instructor, College of Physicians and Surgeons, Postgraduate Medical Extension, Columbia University, New York, New York.
- 3:30- 4:10 Characteristics of the Allergic Child  
NORMAN W. CLEIN, M.D., Director of Children's Clinic, Chief of Pediatric Services, Kings County Hospital, Seattle, Washington.
- 4:15- 5:00 Special Problems in Treatment and Management of Asthma in Children  
M. MURRAY PESHKIN, M.D., Instructor, College of Physicians and Surgeons, Postgraduate Medical Extension, Columbia University, New York, New York.
- 8:00-10:00 Evening Informal Discussion Groups  
ALBERT H. ROWE, M.D., General Chairman.

## EVENING DISCUSSION GROUPS

Wednesday, November 10

8:00-9:00 P.M.

### Food Allergy

ALBERT H. ROWE, M.D., *Chairman*  
ORVAL R. WITHERS, M.D.

### Asthma

HARRY L. ROGERS, M.D., *Chairman*  
ROBERT LOUIS BENSON, M.D.  
MERLE W. MOORE, M.D.

### Laboratory Procedures

GEORGE E. ROCKWELL, M.D., *Chairman*  
ROY MATTERI, M.D.  
FRED W. WITTICH, M.D.

Wednesday, November 10

9:00-10:00 P.M.

Bacterial Allergy

HYMAN MILLER, M.D., *Chairman*

ROBERT LOUIS BENSON, M.D.

HARRY L. ROGERS, M.D.

FRED W. WITTICH, M.D.

Pharmacology and Drugs

FRANK PERLMAN, M.D., *Chairman*

NORMAN A. DAVIS, M.D.

WILLIAM YOUMANS, M.D.

Atopic Dermatitis

A. ROSTENBERG, JR., M.D., *Chairman*

M. MURRAY PESHIKIN, M.D.

ORVAL R. WITHERS, M.D.

Thursday, November 11

*Miscellaneous Manifestations of Allergy*

A.M.

- 9:00- 9:40 Unusual and Obscure Conditions of Allergy  
ORVAL R. WITHERS, M.D., Associate Professor of Medicine, School of Medicine, University of Kansas, Kansas City, Kansas
- 9:45-10:25 Ocular Allergy  
J. WARRICK THOMAS, M.D., Thomas Clinic, Richmond, Virginia
- 10:30-11:10 Physical Allergy  
FRANK PERLMAN, M.D., Assistant Clinical Professor, University of Oregon Medical School, Portland, Oregon.
- 11:15-12:00 Cerebral Manifestations of Allergy Including Aural Allergy  
HARRY L. ROGERS, M.D., Jefferson Hospital Allergy Clinic, Jefferson Medical College, Philadelphia, Pennsylvania.

P. M.

- 2:00- 2:30 Present Status of Antihistaminic Drugs  
GEORGE E. ROCKWELL, M.D., President, The American College of Allergists, Milford, Ohio.
- 2:35- 3:25 Allergic Bronchitis, Bronchiectasis and Loeffler's Syndrome  
HARRY L. ROGERS, M.D., Jefferson Hospital Allergy Clinic, Jefferson Medical College, Philadelphia, Pennsylvania
- 3:30- 4:25 Vascular Allergy  
HYMAN MILLER, M.D., Assistant Clinical Professor of Medicine in Allergy, University of Southern California, Los Angeles, California.
- 4:30- 5:00 Joint Allergy  
ROBERT LOUIS BENSON, M.D., Clinical Professor, University of Oregon Medical School, Portland, Oregon.
- 8:00-10:00 Evening Informal Discussion Groups  
ALBERT H. ROWE, M.D., General Chairman.

EVENING DISCUSSION GROUPS

Thursday, November 11

8:00-9:00 P.M.

Pediatric Allergy

NORMAN W. CLEIN, M.D., *Chairman*

M. MURRAY PESHIKIN, M.D.

Hay Fever

JAMES E. STROH, M.D., *Chairman*

FRANK PERLMAN, M.D.

GEORGE E. ROCKWELL, M.D.

Psychosomatics Related to Allergy

HERMAN A. DIGKEL, M.D., *Chairman*

HYMAN MILLER, M.D.

ALBERT H. ROWE, M.D.

Thursday, November 11

9:00-10:00 P.M.

Contact Dermatitis

HARRY L. ROGERS, M.D., *Chairman*

A ROSTENBERG, JR., M.D.

J. WARRICK THOMAS, M.D.

Mold Allergy

FRED W. WITTICH, M.D., *Chairman*

JAMES E. STROH, M.D.

Urticaria and Angioneurotic Edema

ORVAL R. WITHERS, M.D., *Chairman*

ALBERT H. ROWE, M.D.

Friday, November 12

*Respiratory and Miscellaneous Allergies*

A.M.

9:00- 9:30 The Botany of Hay Fever Plants

JAMES E. STROH, M.D., Assistant Clinical Professor of Medicine, Head of the Department of Allergy, University of Washington School of Medicine, Seattle, Washington.

9:35-10:25 Hay Fever—Diagnosis, Treatment and Management

MERLE W. MOORE, M.D., Assistant Clinical Professor, University of Oregon Medical School, Portland, Oregon.

10:30-11:25 Mold Allergy: Symptoms, Diagnosis and Treatment

FRED W. WITTICH, M.D., Secretary-Treasurer, The American College of Allergists, Minneapolis, Minnesota.

11:30-12:00 Perennial Allergic Rhinitis

ORVAL R. WITHERS, M.D., Associate Professor of Medicine, School of Medicine, University of Kansas, Kansas City, Kansas.

12:05-12:30 Pollen Counts and Demonstration (Photomicrograph Illustrations)

FRANK PERLMAN, M.D., Assistant Clinical Professor, University of Oregon Medical School, Portland, Oregon, and JAMES E. STROH, M.D., Assistant Clinical Professor of Medicine, Head of the Department of Allergy, University of Washington School of Medicine, Seattle, Washington.

P. M.

2:00- 2:55 Pathology of Asthma

WARREN HUNTER, M.D., Professor of Pathology, University of Oregon Medical School, Portland, Oregon.

3:00- 3:50 Basic Principles of Allergy

FRED W. WITTICH, M.D., Secretary-Treasurer, The American College of Allergists, Minneapolis, Minnesota.

3:55- 4:25 Treatment of Status Asthmaticus

J. WARRICK THOMAS, M.D., Thomas Clinic, Richmond, Virginia.

4:30- 5:30 X-ray Diagnosis and Therapy

IVAN WOOLLEY, M.D., Clinical Associate, University of Oregon Medical School, Portland, Oregon.

## NONREAGINIC ALLERGY

M. G. MEYER, M.D., F.A.C.A.

Michigan City, Indiana

THE approach to allergic problems has had many varied routes. Recently the psychosomatic approach is enjoying its heyday, and perhaps justifiably so. If, however, we are content to utilize only the psychogenic equilibrium of the individual as a means to a cure, it is my personal opinion that we are, in reality, then assuming that allergy *per se* does not exist. The greatest deterrent, therefore, to the writing of this paper is the possible criticism that this diagnostic method is also a devious channel to a substitution phenomenon on the patient's part.

We, as allergists, are accepting many unusual and previously unclassified syndromes and illnesses as having an allergic insult as their etiological factor. Coca,<sup>1</sup> several years ago, advanced the opinion that nonreaginic allergy is responsible for many of the unusual patient problems. After two years' study and application of this theory, I believe an attempt at confirmation of his original ideation is indicated.

My enthusiasm for this approach stems from the fact that cutaneous reactions, especially in food sensitivity, fail in such a high percentage of cases that they are valueless. Elimination diets are, of necessity, so discouraging to the patient in the time element involved, that it is difficult to complete a case unless one is unusually lucky in hitting the offending food early. They also fail to take into account that any one food may be the offender and that its ability to consistently provoke an allergic insult is lacking. This latter statement, I am sure, will find agreement among all allergists.

The explanation as to why the cardiovascular apparatus is invariably sensitized is very difficult physiologically. Possibly it is still due to the response of the vascular system to a histamine-like substance, although most opinions are to the contrary. In the same line of reasoning, it is peculiar that, at least in my experience, none of the antihistaminic drugs suppress the allergic reaction or the acceleration of the pulse. Peculiarly, however, histamine given either in fractional daily doses or intravenously does alter the pulse response and does control the symptoms. This is graphically illustrated in Figures 1 and 2.

Figure 1 shows the effect of fractional daily doses, while Figure 2 shows the effect of intravenous histamine in the dosage indicated; it is of interest that this patient, after three months, is still symptom free, although cereal and egg have both been reintroduced into his diet.

Coca has presented good evidence that severance of the sympathetic chain will also alter the pulse response but that it will not consistently remove either the symptomatology or the acceleration phenomenon to all the allergens. It is, therefore, still a confusing issue from a physiologic, pharmacologic basis.



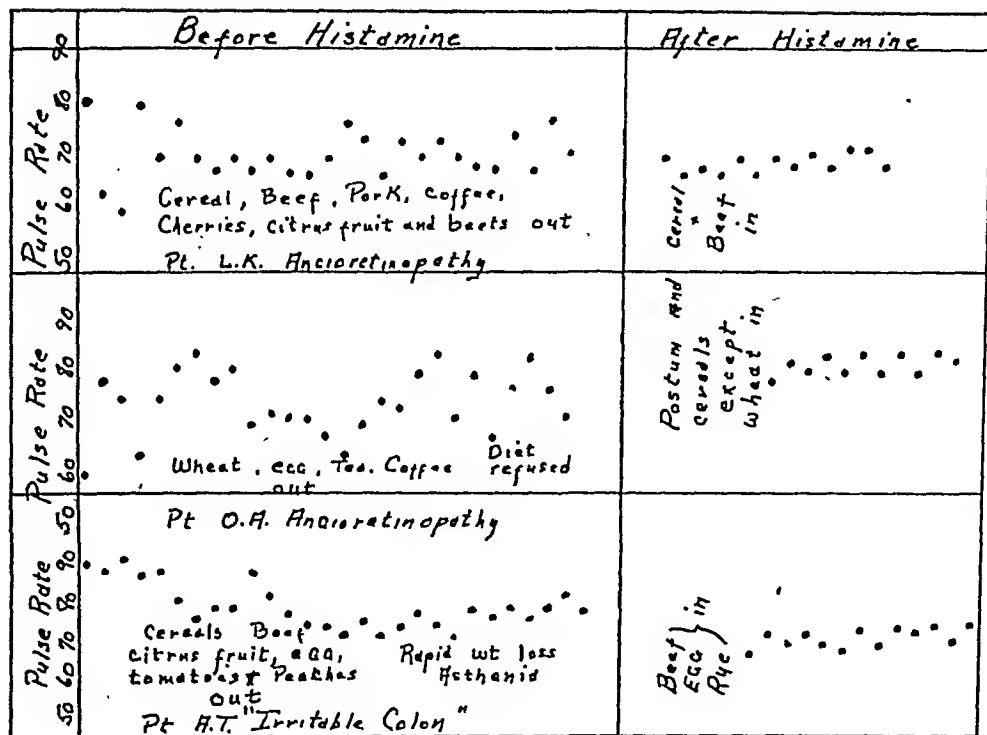


Fig. 1.

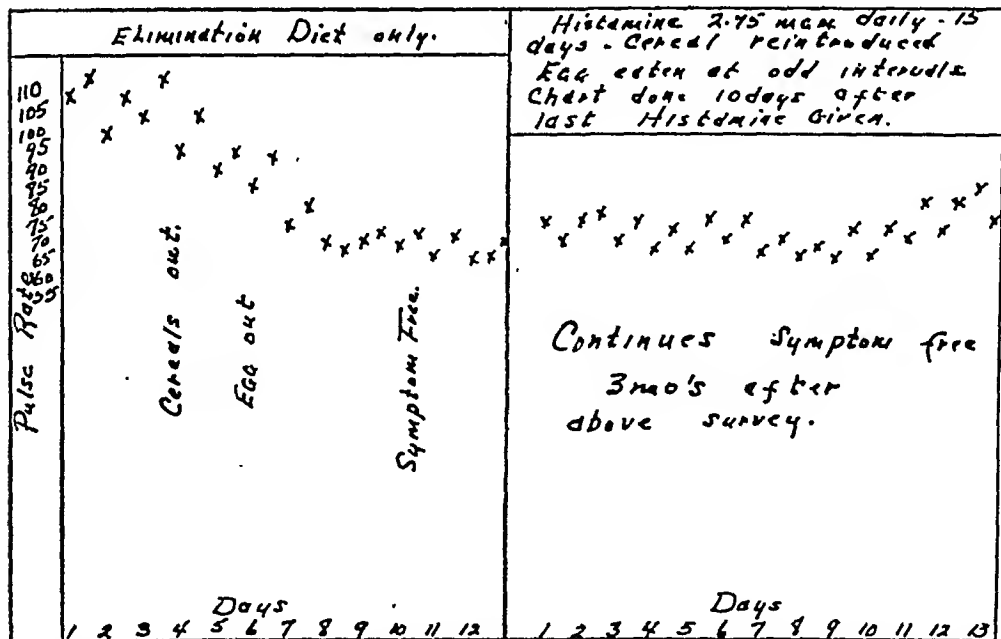


Fig. 2. F.B., aged forty-seven. Gastric ulcer. X-ray and gastroscopic proof. Two-year history. Operation refused.

The method of survey which I have used differs from that employed by Dr. Coca in this respect. I find it difficult to limit the patient accurately to one food per day or one food per meal. As a consequence, I start them off with the following directions:

"The following instructions are given for your convenience in attempting to find the foods to which you are sensitive. It has been shown that most illnesses which are not caused by infections are generally the result of sensitivity to food or contacts.

"It must be clearly understood that unless these instructions are followed in exact detail, you are wasting your time as well as mine.

"The importance of accurately counting the pulse cannot be overemphasized. The valuation of a few points may alter the accuracy of the test since the whole principle of this procedure depends on accurate records. Proceed as follows:

"1. On the day before the test diet is started, eat nothing following the noon meal, and count the pulse at 4:00 p. m., 8:00 p. m., and 9:00 p. m. Instructions for counting pulse are on the reverse side.

"2. Count the pulse on awakening before getting out of bed.

"3. Count the pulse just before each meal.

"4. Count the pulse one-half hour, one hour, and one and one-half hours after each meal. Always sit down and rest for two minutes before taking pulse.

"5. On the first two days of the diet eat the menu on the accompanying chart exactly. Do not add any articles to it until you have either phoned me the pulse readings or given them to me in person. Salt may be used as desired.

"6. Prepare all foods in either glassware or enamelware rather than aluminum.

"7. Keep the chart as indicated on the accompanying sheet.

"8. List all symptoms noted, such as headache, indigestion, excessive gas, joint pains, diarrhea, vomiting, heart consciousness, constipation, et cetera."

These instructions may seem rather dramatic in their presentation to the patient, but drama appeals more to the average person than simple statement of fact and they are more apt to co-operate fully. I will delete the use of enamelware rather than aluminum on my next set of instructions since I, personally, have failed to find instances of aluminum sensitivity. Dr. Coca shows evidence that it exists. The importance of physical and mental rest during the pulse-counting interval must be impressed. Whether or not one is wrong in having the patient count his own pulse, I do not know. Certainly, hospitalization for the average individual, without complete necessity for daily observation, is hardly indicated in these times. I must also say that I am very hesitant to put all suspected allergic patients on this survey, because in some instances I have sensitized them to their radial pulse to a much greater degree than to food or contact. If the patient's symptoms are severe enough, they will co-operate well. If they are only of a mild to moderate annoyance, they will not subject themselves to the details involved. If the decision to utilize this method has been made, the following diet is given for two successive days:

# NONREAGINIC ALLERGY—MEYER

Pulse rate 4:00 p. m. Day before test starts		8:00 p. m.	Before arising 9:00 p. m. Day of test
<i>Menu</i>	<i>Pulse Rates</i>		<i>Symptoms</i>
Rice	Before		
Milk	½ hr. after		
Sugar	1 hr. after		
Grapefruit	1½ hr. after		
Beef	Before		
Peas	½ hr. after		
Potatoes	1 hr. after		
Lettuce (No dressing)	1½ hr. after		
Pears (Water packed) or Fresh Apple			
Rice	Before		
Sugar	½ hr. after		
Milk	1 hr. after		
Butter	1½ hr. after		
Cheese			
<i>Second Day</i>		<i>Pulse before arising</i>	
Whole wheat bread	Before		
Milk	½ hr. after		
Butter	1 hr. after		
Egg	1½ hr. after		
Beef	Before		
Carrots	½ hr. after		
Lettuce	1 hr. after		
Beets	1½ hr. after		
Whole wheat bread	Before		
Peas	½ hr. after		
Chicken	1 hr. after		
Grapefruit	1½ hr. after		

I do not believe it is any better and probably not as good as other individuals will work out for themselves. I have accustomed myself to interpret it, and for that reason use it. My line of reasoning in this diet is as follows: The breakfast on this first day is aimed primarily at milk and citrus fruit. If the former, there is a chance for a recheck at supper of the same day, and if the latter, a recheck for supper of the second day. Rice and sugar, in my experience, are uncommon allergens. I have one patient sensitized to cane sugar and not to beet sugar, and only four who are sensitized to all cereals, including rice. Dinner of the first day eliminates

cereal and milk, and if a pulse response occurs here, an opportunity for a recheck on peas, a fairly common allergen, is given at the second dinner. If beef or potatoes seem indicated, a recheck at the second supper is possible, provided citrus fruit has not been incriminatory. The first day's

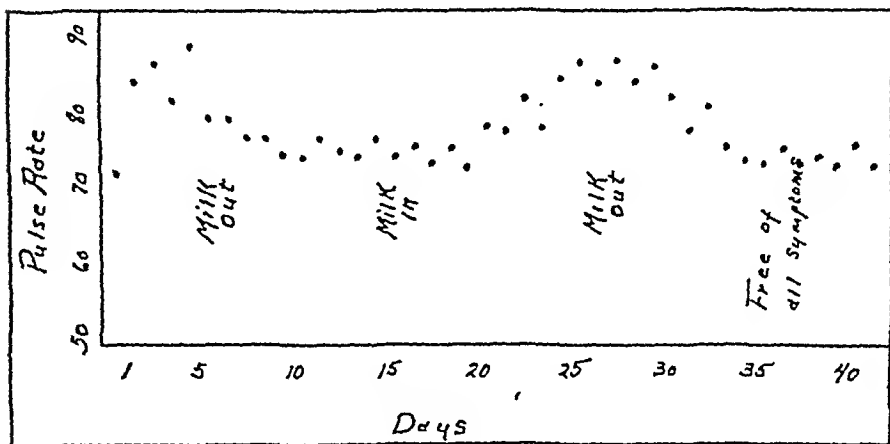


Fig. 3. C. S., aged forty. Clinical peptic ulcer. X-ray proof.

supper is obviously pointed at dairy products, and if the patient is sensitized to the same, a marked pulse response is almost always obtained here. Breakfast of the second day introduces both egg and wheat, very common allergens. Opportunity for a recheck of wheat has been given on the previous day and is repeated at the second day's supper. The second dinner eliminates potatoes, occasionally encountered, and gives an opportunity to check a delayed reaction to beef since carrots and lettuce are also uncommon allergens. The supper of the second day introduces fowl, which is easily spotted if no previous tachycardia has been registered. Since dairy products, wheat, egg and citrus fruit are, in my opinion, the most common of food allergens, my primary interest in these two days centers on these foods. Obviously, from this point on, addition or subtraction of foods, introducing one new one per day, allows us to continue the survey intelligently.

The application of this method should not be attempted unless one has thoroughly acquainted himself with the chapters of Coca's book indicating the difficulties of interpretation. They exist to such an extent that I have had to abandon many patients simply because I could not identify the pulse accelerator. These difficulties are briefly reviewed. Figure 3 indicates the latent period of temporary loss of sensitivity. It will be noted that after primary elimination of milk, with its reintroduction there are four days before a pulse acceleration occurs, and that the resultant tachycardia persists for forty-eight hours after milk is eliminated, the latter being known as the carry-over reaction.

# NONREAGINIC ALLERGY—MEYER

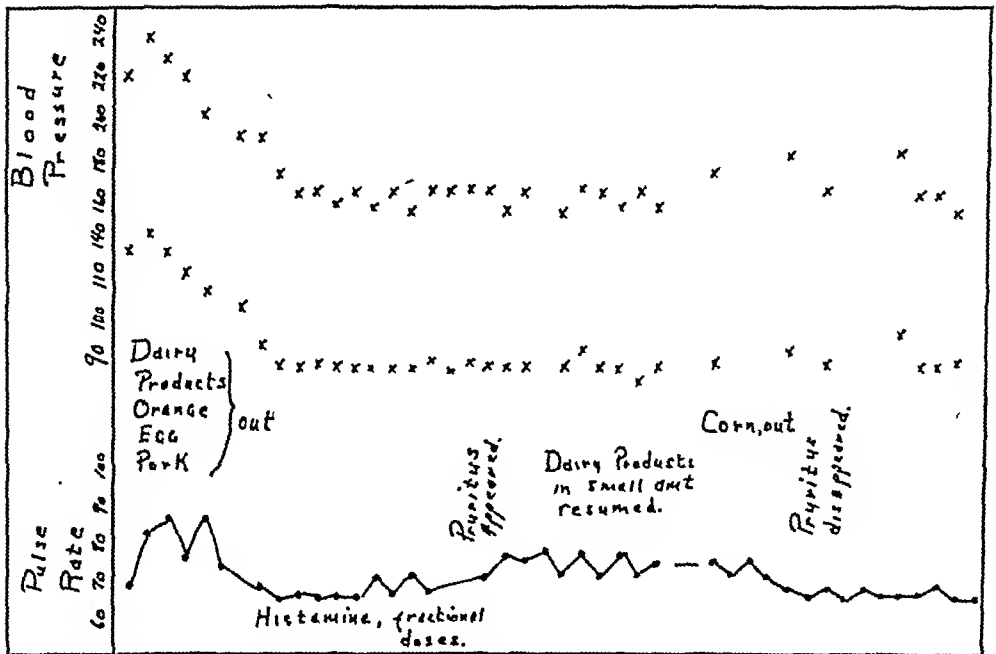


Fig. 4. F. M., aged sixty. Hypertension was relieved, then followed by pruritus, which was relieved.

Figure 4 shows the importance of major and minor allergens. This patient first experienced dramatic relief following the removal of the primary allergen, only to have a new allergic symptom manifest itself later. Removal of corn then cleared the pruritus. This may indicate the specificity of allergens.

The sensitivity to a large number of foods, or at least a continuous pulse elevation, is seen quite often. Care must be taken to rule out the effects of known or unknown inhalants or contacts. The latter is shown graphically in Figure 5. It is readily seen that the hypertension and the relative tachycardia were controlled perfectly while these patients were ambulatory in the hospital, and with the same degree of activity were not controlled on return home.

The specificity of allergens is an interesting phenomenon, and another illustrative example is given in Figure 6. The elimination of dairy products relieved the arthralgia. The elimination of wool contacts relieved the asthma, and although a tachycardia to potatoes persists, no symptoms were gained from their use. This patient, however, was operated upon for endometriosis one month ago, but I refuse to draw conclusions from that.

It is worth repeating that not all patients are candidates for this type of survey. I consider the following factors:

Is the patient of a relatively stable personality, without too much evidence of vasomotor instability?

Is he willing to forego his pleasure in food ingestion to follow this program carefully?

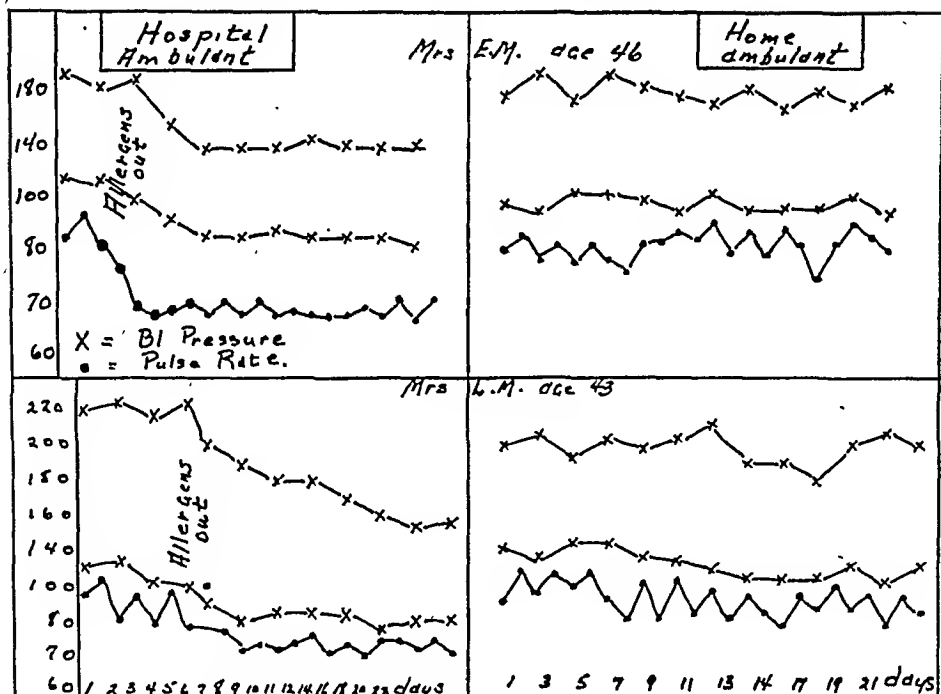


Fig. 5.

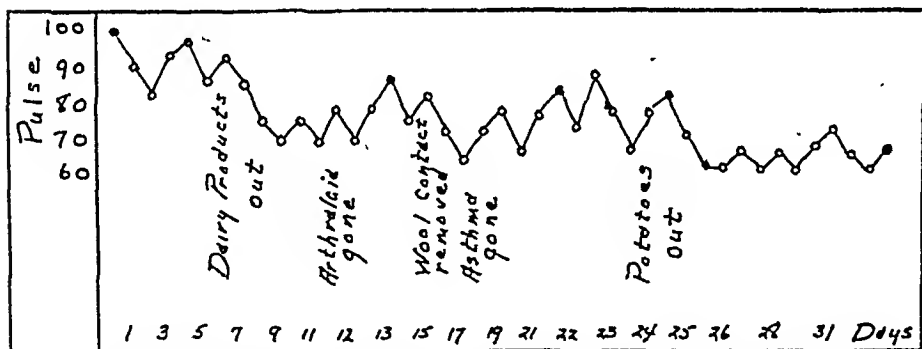


Fig. 6. C. K., aged thirty-eight. Arthralgia, asthma. After three weeks of eliminating potatoes, patient is reingesting them since she has no subjective symptoms from eating them.

Is his patience sufficient to give the allergist several weeks of a carefully followed routine?

Is he intelligent enough to realize that the analysis does not always result in success?

If the problem is solved, is he of the type that would be willing to continue on a restricted program?

That these patients represented cures based on allergen removal is considered only if the following axioms are met:

1. That there is a personal and familial history of a similar situation or an illness for which no definite etiological factor has been previously attributed.
2. That these symptoms have disappeared and reappeared as the foods involved were eliminated and reingested.
3. That with the ingestion of these foods, an accelerated pulse is manifest if extraneous conditions are controlled.

The total number of patients in whom a successful result was obtained by the methods previously outlined are shown in the following review :

Irritable Colon Syndrome .....	20
Peptic Ulcer .....	2
Ulcerative Colitis .....	1
Migraine .....	13
Ménière's Disease .....	6
Chronic Rhinitis .....	4
Retinal Angiopathies .....	3
Urticaria .....	7
Epileptiform Seizures .....	5
Paroxysmal Tachycardia .....	5
Angina Pectoris (with EKG changes) .....	3
Chronic Asthmatic Bronchitis .....	4
Emotional Instability and Depressions .....	8
*Multiple Sclerosis .....	2
Hypertension .....	24
Myalgias .....	3
Pruritus Ani and Vulvae.....	6

Total .....116

Hypertension presents a challenge. It continues to lead the parade as a cause of death in the United States. Certainly any procedure which not only reduces the pressure but seemingly prevents the complications which give an untimely end to these people is worth a trial. The total number of hypertensives attempted on this management is forty. Control in twenty-four represents an incidence of 60 per cent. This compares favorably with the rice and fruit juice diet, which may represent exactly the same method of treatment. Control is regarded if the diastolic pressure is below 100 after it has consistently been above 100 prior to elimination therapy. The average diastolic pressure of those treated is now 86. Table I shows six typical examples of patients who have been followed longer than eighteen months and who continue to be well controlled, and in whom, as in the other eighteen, no complications involving progressive renal or cardiac damage have been noted.

Although it is generally agreed that when renal damage exists to a degree recognizable by laboratory procedures, little can be offered, I should like to mention two patients who have had both clinical and laboratory improvement following elimination therapy. This is shown in Table II.

\*Multiple sclerosis is a long and unpredictable illness. The patients mentioned have had a remission for better than fifteen months, but conclusions cannot be drawn from that at this time. Diabetes mellitus was originally placed on this chart and then removed. Three mild cases have been controlled for over a year without insulin and with the elimination of foods that were not necessarily high in carbohydrate value. However, any diabetic, knowing that he has the illness, is very apt to eliminate foods excessively high in carbohydrates as a matter of precaution.

# NONREAGINIC ALLERGY—MEYER

## TABLE I

Name	Age	Previous Blood Pressure (6 or More Readings, Avg.)	Present Blood Pressure (10 or More Readings, Avg.)	Allergens	No. of Months Followed
Mrs. P.M.	52	190-S 110-D	140-S 86-D	Beef, peas, str. beans, tomatoes, spinach	22
Mrs. S.R.	64	220-S 130-D	160-S 90-D	Eggs, celery, citrus fruit, apples	21
Mrs. M.M.	58	190-S 110-D	150-S 84-D	Potatoes, beef, peas, str. beans	21
E.P.	40	166-S 100-D	142-S 84-D	Citrus fruit, cane sugar, fish	21
Mrs. J.F.	47	180-S 120-D	146-S 80-D	Eggs, pork, coffee, choc., chicken	21
J.D.	38	158-S 100-D	130-S 76-D	Chocolate	21

## TABLE II

Name	Before Allergens Out			After Allergens Out		
	B.P.	Urine	Chemistry	B.P.	Urine	Chemistry
Mrs. E. L. Age 36 Dizziness Headache Exertional Dyspnea Heart conscious		Sp. Gr. 1.004 Alb.-Tr.	NPN-48		Sp. Gr. 1.016 Alb.-0	NPN-32
	250/140	Micro. 3-4	Urea N.-30	160/88	Micro. Amorph. urates only	Urea N.-18
	230/136	Hyaline	PSP	158/81		PSP
		1-2 granular HPF	1 Hr.-20% 2 Hr.-22%	158/82	Only occasional headache now	1 Hr.-40% 2 Hr.-16%
Mrs. S. R. Age 62 "Palsy" Dizziness Exertional palpitation Angina Dyspnea		Sp. Gr. 1.006 Alb.-+	NPN-52		Sp. Gr. 1.014 Alb.-spt.	NPN-40
	210/130	Micro. 7-8	Urea N.-32	170/90	Micro.	Urea N.-20
	220/134	Hyaline	PSP	172/88	1-2 Hyaline	PSP
		4-5 granular HPF	1 Hr.-28 2 Hr.-18	168/88	HPF	1 Hr.-40 2 Hr.-20
					Dyspnea only-T with marked exertion	

## TABLE III

Name	Age	Average Frequency of Attacks	Grand Mal	Frequency	Medication As Before
B. B.	24	3 times weekly	+	3 times weekly	+
L. C.	19	5 times yearly	+	2 times in 15 mos.	+
L. N.	34	2 times monthly	+	1 time in 4 mos. known diet indiscretion	0
M. M.	62	2 times monthly	+	1 time in 6 mos.	0
C. T.	64	3 times weekly	+	2 times in 10 mos.	½ dosage Dilantin S
L. S.	26	3 times daily	0	3 times daily	+
E. P.	58	4 times monthly	0	1 time in 6 weeks	No medication

Gastrointestinal complaints, when functional, I believe, are all of allergic origin. I admit the etiological factor of nervous tension but, as in all allergies, I believe that the trigger mechanism would not be effective if the



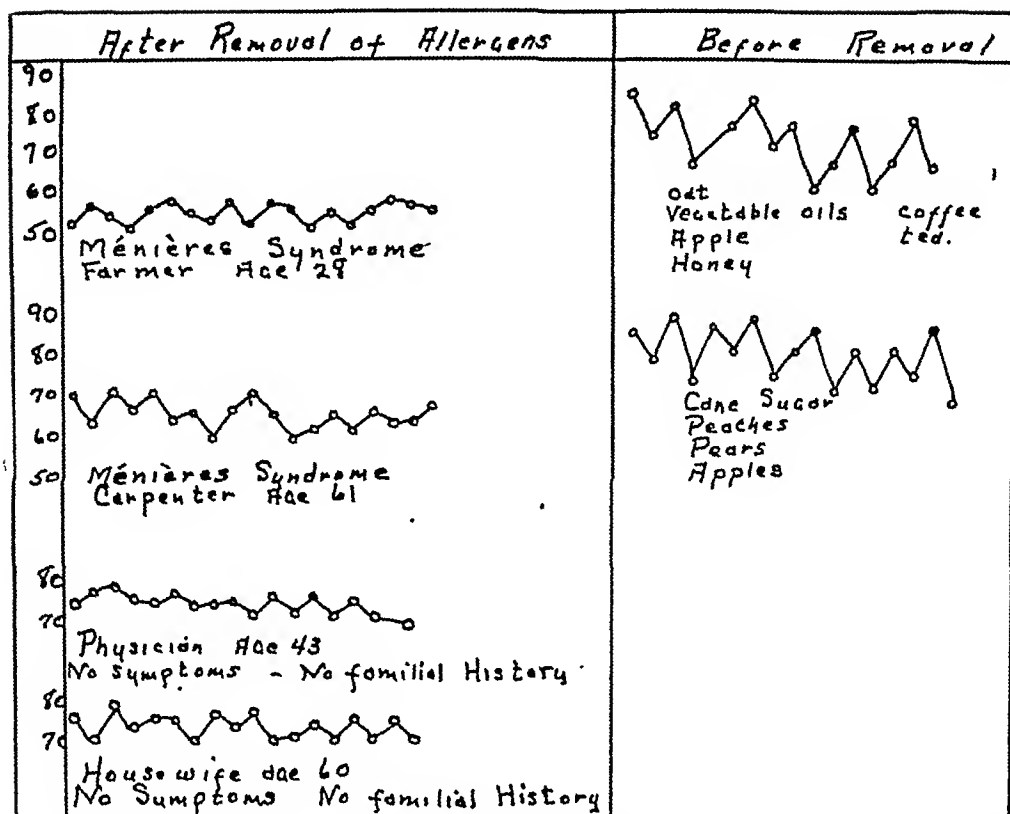


Fig. 7.

individual were not of an allergic diathesis. Certainly all high-tension individuals do not have a bellyache.

Twenty-five successive cases with gastrointestinal complaints were studied by our group. Of these twenty-five, nine showed clinical and x-ray evidence of organic disease, such as cholelithiasis, peptic ulcer and malignancies. Of the remaining sixteen, fifteen are completely free of symptoms following the removal of foods which caused a relative tachycardia. In addition, two patients with peptic ulcer, proven radiologically, have had both subjective and objective cure by the elimination of offending foods.

That the nervous system is often the shock tissue is an accepted fact. Experience with epileptiform seizures are shown in Table III. These are not good results but do indicate some specificity. At least in most of them, the medication has been reduced and the number of attacks have been greatly lessened.

Ménière's Syndrome and its relief are illustrated in Figure 7. This is also shown as an indication of how well pulse stability is attained in the individuals after elimination of foods has been accomplished, and how relatively stable the pulse is in two individuals in whom no symptoms appeared which might possibly be interpreted as allergic.

A rather large number of migraines have been well controlled. A typical migraine case is as follows:

Mrs. E. B., aged thirty-seven, with a typical unilateral headache associated with visual disturbances, occurring two to four times monthly, was seen with an entrance complaint of pruritus vulvae. The headaches were regarded by this patient as incurable and were not mentioned in the original complaints. After the elimination of milk, she volunteered the information that she had had migraine which has disappeared entirely. The pruritus, in turn, had not disappeared, and it was only after energetic treatment for the trichomonas infection by another member of our group that the pruritus disappeared.

Cephalalgias not necessarily of a migraine type are also worth investigation, as illustrated by the following case report:

D. B., aged twenty-two, has had severe headaches following his discharge from the army, where he had had a rather severe cerebral concussion following a land mine explosion. Complete neurological examination and spinal fluid examination were negative for pathologic conditions. This patient, however, showed a pulse rate rising from 64 to 110 every time eggs in any form were ingested. After the elimination of eggs on October 10, 1947, he has had no headaches and is working as a laborer in a construction company.

Peculiar myalgias and arthralgias failing to fit any category are often seen. An eosinophilia is suspicious. The sedimentation rate may be normal or elevated. A low grade fever is possible. Cardiographic evidence of rheumatic heart disease is lacking. The patients are chronically and painfully disabled. They are worth a trial. A previous chart showed disappearance of arthralgia in an individual following the elimination of dairy products. Another case history represents rather a dramatic cure:

S. H., aged nineteen, had been hospitalized elsewhere for over four months with arthralgia and myalgia. She had a sedimentation rate of 14 to 20 and a persistent eosinophilia of 6 to 8 per cent. Numerous muscle biopsies were negative for trichinosis. One consultant had suggested allergy, and histamine in large doses had been given, with rather dramatic relief when given two to three times daily. Two weeks of study revealed a pulse acceleration to walnuts, pork and egg. Within seventy-two hours following the removal of these allergens, symptoms subsided. The young lady has returned to school, is taking part in her class play and is planning to continue her studies as a physical education major.

In conclusion, then, my personal opinion is that this pulse dietary method of diagnosis is a distinct weapon in the armamentarium of allergists. However, it is not the answer. It is too time-consuming for both physician and patient. It is too difficult for the average patient to eliminate common foods, which unfortunately seem to be the most common allergens. I have indicated that intravenous histamine may be the answer. Yet, it too is not simple enough for the average patient. Antihistaminics are not the answer to date, and severance of the sympathetic chain is too hazardous an approach to the problem for the average patient.

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## CONTROL OF ALLERGY TO ANTIRABIC VACCINE

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SINCE the institution of vaccine therapy for the protection against rabies, numerous reactions have been reported due to the vaccine used. These reactions have ranged from the simple swelling at the site of the injections to the dangerous neurological symptoms of ascending paralysis and involvement of the brain, with death.

At the first rabies conference of the League of Nations, Remlinger<sup>5</sup> reported an incidence of severe reactions to the Pasteur treatment of 329 in 1,164,264 treated victims of dog bite. McKendrick,<sup>6</sup> since that time, also reported thirty-three cases in 175,000 people treated. The incidence of severe reactions reported by numerous state health departments averages about 0.083 per cent with mortality between 10 per cent and 16 per cent. These statistics reveal the seriousness of the situation prevalent today.

Many theories have been advanced to explain these reactions. The controversy regarding the etiology of the paralysis has been present since the institution of vaccine prophylaxis. Babes<sup>1</sup> expounded the theory that the reaction was due to the rabies toxin and its predilection for nerve tissue. Koch<sup>5</sup> believed the paralysis was due to the canine rabies and not the vaccine. Many investigators were of the opinion that the reaction was due to a fixed virus. Prausnitz<sup>7</sup> believed that the reaction was due to the injection of heterogenous nerve substance in especially predisposed susceptible people. In 1918, Cornwall<sup>3</sup> concluded that the reactions were allergic in nature, resulting from the injection of foreign nerve substance (protein). Schwenther and Rivers,<sup>9</sup> in 1934, discovered that brain tissue under proper conditions functions as a complete antigen, and is capable of exciting in rabbits the development of complement-fixating antibodies, which are organ-specific rather than species-specific. In 1936, Burky and Henton<sup>2</sup> found that repeated injections of lens extract plus staphylococcus toxin gave rise to a skin sensitivity to lens extract, and that if the lens of a sensitized animal was injured by needling, there developed an intra-ocular inflammation which clinically and histologically resembled endophthalmitis phaco-anaphylactica. This inflammation was believed to be due to the absorption of lens protein by the hypersensitive subject. They devised a method of desensitization, using the lens extract and staphylococcus toxin. The eye improved as the animal lost skin sensitivity. This showed that a reduction of skin sensitivity also produced a reduction in organ complement-fixing antibody reaction.

In 1939, Horak<sup>4</sup> reviewed the literature carefully and presented many cases of rabies vaccine reaction. He revealed that an allergic reaction was present in 87.5 per cent of the paralytic cases, and in 33 per cent of those cases which did not develop neurological symptoms. He also classified the

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reactions into six groups and advised gradual desensitization to the vaccine to prevent the allergic skin reaction. He reasoned that the prevention of the skin allergy would prevent the neurological sequelae which can prove fatal. Because his classification is so all-inclusive, it bears repetition:

Group 1.—Cases which develop a generalized urticarial rash, which respond to epinephrine promptly. There is no mortality in this group, and a history of previous injections may be obtained.

Group 2.—Delayed reactions of the tuberculin type, which occur at the site of the injections. These are most common and are not serious.

Group 3.—Reactions similar to Group 2, but much more severe and frequently associated with fever, headache, nausea and generalized adenopathy. Each injection is apt to cause redness at site of previous injection. This group is prone to develop paralysis, and caution should be used.

Group 4.—Simple neuritis involving the peripheral and cranial nerves, the facial nerve being the most commonly involved. The paralysis is usually transitory.

Group 5.—Dorsal lumbar myelitis most often occurring during the second and third weeks of treatment, and characterized by the gradual onset of fever, weakness, and terminating in paralysis, particularly of the lower extremities. There is also numbness and tingling of the lower extremities and sphincter disturbances preceding the paralysis. Local reactions of Group 3 are frequently present. The mortality rate is low in this group.

Group 6.—Paralysis of the Landry type—sudden in onset, often with high fever, nausea and headache, girdle pains, retention of urine, insomnia, and ascending paralysis. In one-third of the cases, bulbar paralysis ensues and death occurs. The local reactions are of Group 3.

Thomas,<sup>10</sup> in 1944, also reviewed the literature and presented a case of paralysis, following antirabic vaccine therapy which apparently responded to large doses of vitamin B<sub>1</sub>.

In view of the evidence pointing towards the allergic etiology of these vaccine reactions, it was decided to attempt inhibition of the skin reactions by the use of the recently proven antihistamine drug, Benadryl. Since it is possible to prevent generalized organ-specific reactions in sensitized subjects by desensitization of the skin, the use of such a drug to prevent skin reactivity and generalized allergic reactivity seemed logical. In the following case report, the drug undoubtedly suppressed the allergic reaction to the vaccine used.

#### CASE REPORT

On May 3, 1947, Dr. Elmer Amerman, a pediatrician, referred a ten-year-old boy, A. T., Jr., for antirabic vaccine prophylaxis. The possibility of an allergic reaction presented itself because of a positive family history, so that extreme caution had to be exercised while giving the inoculations. This boy had sustained a rat bite to

his right index finger five days previously. The wound had been cleansed and washed, and a local physician had injected 300,000 units of penicillin (Romansky formula) intramuscularly, on the same day and on the following day.

Because of the prevalence of endemic rabies in wild rats, it was deemed essential that the patient be given prophylactic antirabic therapy. Lederle's Semple vaccine was obtained, and the first injection of 2 c.c. was given under the skin into the interscapular region. After the second daily injection the boy developed severe generalized urticaria. Benadryl was instituted in the dose of 50 mg. three times daily. This produced some drowsiness but completely controlled the generalized urticaria. The following injections were easily tolerated during Benadryl therapy. After the fifth injection, the patient stopped the drug voluntarily, and then developed a marked flare-up at each injection site with headache, nausea and slight fever. The drug was immediately resumed and 100 mg. caused the reaction to subside almost completely. The remaining injections were given, and no neurological symptoms developed. The Benadryl was continued for several days and then stopped. No further allergic reaction was manifest up to this time.

In order to prove that the reaction was not due to the previous penicillin used, a repeat test was done which did not elicit any allergic response. A repeat test of Semple vaccine, however, reproduced a flare of the previous injection sites, proving that the vaccine was the only offender.

## COMMENT

According to Horak's classification, this case belongs to Group 3, in which neurological complications can frequently follow. There is no doubt that Benadryl inhibited the skin allergy and so probably prevented more serious sequelae. If this can be accomplished with such simple medication, the use of skin desensitization seems cumbersome and time-consuming. Whether this method of preventing the skin reactions is completely efficacious in preventing the neurological complications, remains to be proven by further study of thousands of cases.

## CONCLUSION

Benadryl can inhibit the skin reactions to antirabic vaccine.

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## A FALL-POLLINATING RED BERRY JUNIPER

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PREVIOUSLY recognized cedar hay fever in the Southwest usually begins about mid or late December and lasts until late February. It is caused by pollen from *Juniperus ashei*—sometimes referred to as *J. Sabinoidea*, *J. Mexicana*, or *J. tetragona*. The common name of "mountain cedar" is often applied, but it is not a species confined to the mountains, and thus this is a misnomer.

The purpose of this paper is to describe a type of cedar not hitherto known to produce hay fever. As early as 1933, Hulsey<sup>4</sup> reported cedar pollen in Fort Worth, Texas, in November. Sellers,<sup>10</sup> farther west in Abilene, noted cedar pollen in the air in the latter part of September. Apparently, however, no one knew the exact origin of this pollen. It did not occur in very large amounts, although Sellers found significant quantities of it, and he felt that it was producing definite symptoms in his cedar-sensitive patients. In pollen counts for ten years in Abilene, he reported high cedar counts in October, diminishing in November, almost disappearing in early December, and again reaching high peaks in the latter part of December, continuing through January and part of February. Thus, there seemed to be two separate cedar seasons, as indeed there are.

In 1937 we first discovered that there was a cedar which pollinated in the months of October and November. It was called to our attention by patients living in southwest Texas who had hay fever at that time, and they definitely were able to associate their symptoms with this period of cedar pollination. Following this observation, we have encountered other patients who have hay fever due to this cedar.

Subsequently, in 1946, Mr. T. R. Stemen<sup>11</sup> identified this as a distinct species of cedar which was originally described by Sudworth<sup>12</sup> in 1905. It was called by him *Juniperus Pinchoti* in honor of Mr. Gifford Pinchot who at that time was professor of forestry at Yale, and later became governor of Pennsylvania.

In seeking further information about this species of cedar, we found that Mr. S. E. Wolff,<sup>13</sup> U. S. Department of Agriculture, had been making a study of it for many years. The map, showing its distribution in more than sixty counties of Texas (Fig. 1), and the following botanical description (Fig. 2) were compiled by him:

*Habit*.—An open spreading shrub, with several semi-prostrate (nearly upright in good sites on the eastern side of its range) stems 3 to 12 feet or even 18 feet tall, with a maximum diameter of 8 inches. No central stem develops. The stems at the groundline develop a prominent bud zone, or stem collar. This shows up early in the life of the seedling as a ring of buds. As the stems increase in diameter and

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## RED BERRY JUNIPER—WOLF

more wood forms more buds are initiated until a bulge as large as a man's head may develop. Sprouts from this collar or bulge elongate whenever some or all the old stems are cut or burned off.

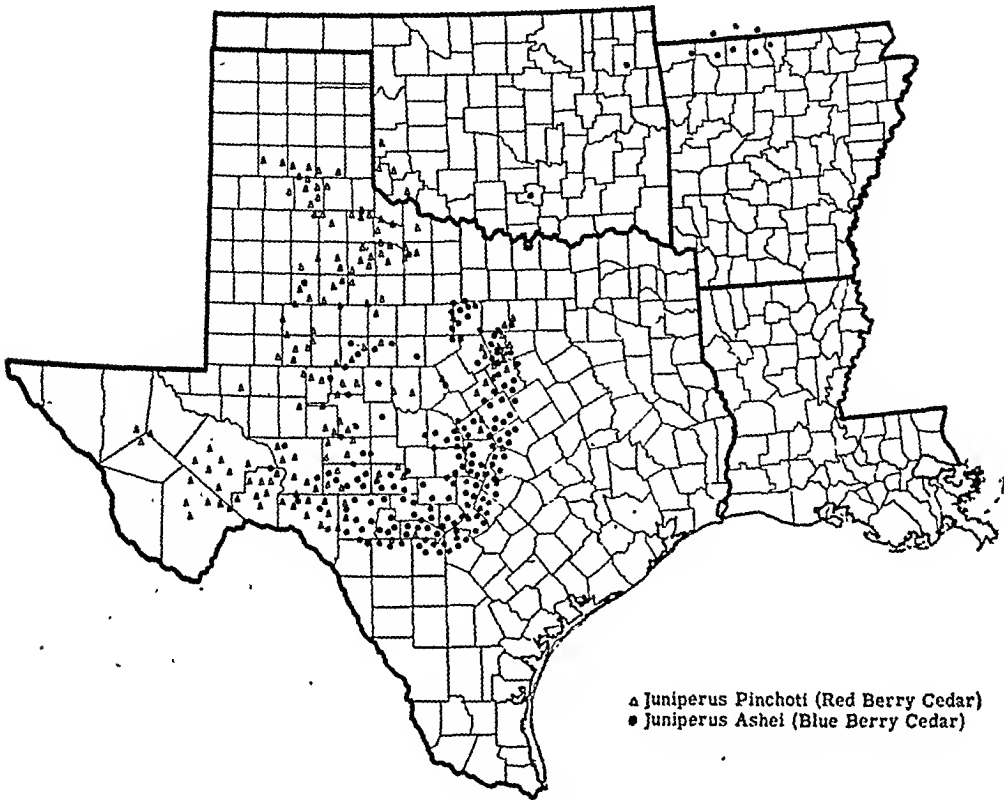


Fig. 1. Juniper distribution in the Southwest.

*Leaves.*—Opposite or in threes, thickened, rounded and glandular on the back, denticulately fringed, drab-green in a mass, on vigorous shoots very slender, thin and sharp-pointed, the gland elongated and resembling a midrib. The glands on the one and two-year-old wood rupture easily, leaving a white spot of wax when dry.

*Flowers.*—On separate plants. Pollination occurs from late September to late November.

*Fruit.*—Copper-red or reddish brown, globe-shaped, ripe one year after being pollinated, very variable in size, averaging  $\frac{1}{4}$  foot in diameter, with thin skin and thick, mealy or juicy, sweet flesh and one or two seeds. Seed egg-shape; very blunt or truncate at apex, upper part lustrous brown and marked with several grooves above the two-lobed, prominent, speckled hilum. Embryo with two cotyledons.

*Twigs.*—Usually reddish in the fall, thick on slow-growing wood, slender and often drooping when rapidly elongating.

*Bark.*—Thin, persisting as thin anastomosing scales.

*Wood.*—Heartwood brown or light brown. Sapwood nearly white.

*Habitat and Distribution.*—Rocky hills, stream breaks, valleys and divides in alkaline soils from Fort Worth, Texas, south to Bandera and Uvalde Counties, west to

## RED BERRY JUNIPER—WOLF

near Alpine, Texas, and northwest into southwestern Oklahoma and the lower Panhandle of Texas. Largest known areas in Texas by groups of counties are in Hood, Bosque and Somervell Counties; Val Verde, Crockett, Terrell, Pecos, Irion, Tom Green and Schleicher Counties; Glass Mts, Coke, Sterling, Howard, Mitchell,

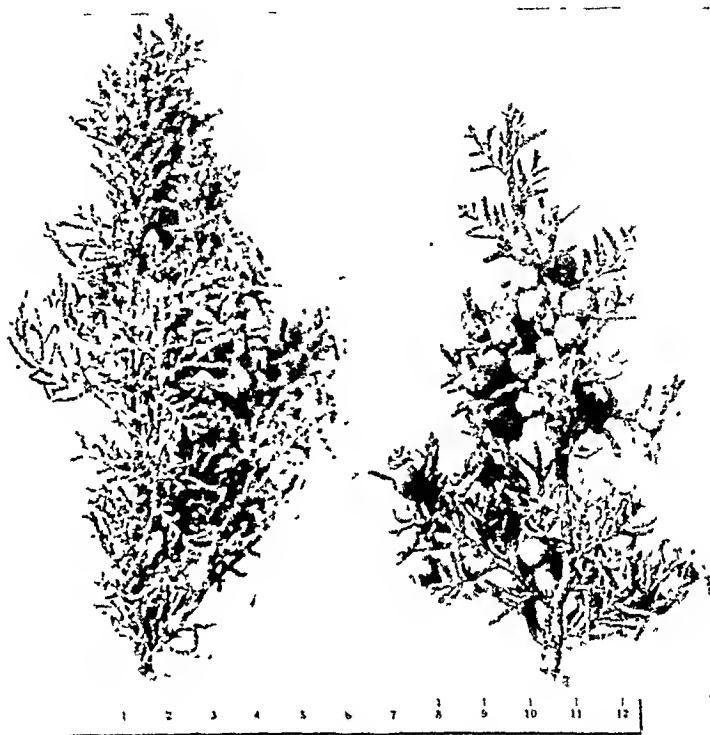


Fig. 2 Branches of male and female *Juniperus Pinchoti*.

Nolan and Taylor Counties; Garza, Kent, Stonewall, Crosby, Dickens, King, Knox, Foard, Cottle, Childress, Hall, Briscoe, Armstrong and Randall Counties. The largest areas lie west and north of the main body of mountain juniper. There are approximately 8,000,000 acres of redberry juniper in Texas.

Physically, the most outstanding differences between this and the post or mountain juniper of central Texas are: (1) it has red, not blue-black, fruits with a waxy bloom; (2) the pollination period is from late September to late November, not from December 10 to February 1; (3) the plants never have a central stem; mountain juniper usually has a central stem; (4) the glands of the leaves rupture leaving spots of white wax; they never rupture in the mountain juniper; (5) when the stems are cut, or burned off, new ones sprout from the bud zone or stem collar near the groundline; mountain juniper never sprouts.

We believe the above description is somewhat more accurate than that given by Sargent<sup>9</sup> in his *Manual of Trees of North America*, particularly in that Sargent failed to mention the bud zone or stem collar just above or at the groundline. This feature was not overlooked by Sudworth in his original description.



## RED BERRY JUNIPER—WOLF

The pollen grains are uniform in size and spheroidal when moist. Upon drying they shrink and collapse irregularly. Grains when moist are 25 to 28 microns in diameter, and when dry 22 to 23 microns. In general they resemble *J. ashei*, but are somewhat larger.

We feel that there is a very close antigenic similarity between the blue berry and the red berry junipers. They may be antigenically identical. Kahn<sup>6</sup> and Black<sup>1</sup> have shown the very close antigenic relationship between two cedars which are botanically much less related than are the two under discussion. However, we have encountered at least two patients who have cedar hay fever only when the red berry cedar is pollinating, and these patients got better results from hyposensitization to the Pinchot cedar than they did when treated with the ashei extract.

Skin tests show a close parallelism, but just as there are variations in the degree of reaction to the various grasses and ragweeds, so there is some variation in the response to skin tests to these cedars. For practical purposes, we feel that the antigenic relationship is close enough to consider the extracts interchangeable in testing and treatment.

The fall-pollinating species is not as abundant as the winter-pollinating species of cedar and hence is not so great a problem in the eastern part of the Texas cedar belt. However, in several areas of southwest and west Texas, Pinchot cedar is present in much larger quantities than ashei, and it is increasing materially both in density and in area. It promises to increase even more—for while other cedars can be killed by burning over or by cutting above the ground, Pinchot cedar readily regenerates from roots or stump. Hence, we may find an increasing amount of hay fever from this cedar. Also, if it becomes widespread, it will extend our cedar pollen season from the latter part of September, when red berry cedar begins to pollinate, to the latter part of February, when blue berry cedar pollination ends.

### SUMMARY

A cedar, the red berry juniper (*Juniperus Pinchoti*, Sudworth), has been found pollinating from late September through November, and is known to cause hay fever. Its distribution includes central and western Texas and adjacent Oklahoma.

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(Continued on Page 441)

# ECZEMATOUS CONTACT DERMATITIS DUE TO STREPTOMYCIN

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VARIOUS types of "toxic erythemas" have been reported following the injection of streptomycin,<sup>1</sup> but, thus far, no instance of eczematous contact dermatitis has been noted.<sup>‡</sup> We are therefore recording an example of the latter type of sensitization, in which the evidence pointed definitely to streptomycin as the cause. Involved in such sensitization are some points of considerable interest.

## CASE REPORT

A nurse, sixty-three years old, had worked in a sanatorium for tuberculosis since April, 1946. In the early part of December, 1946, an eczematous eruption appeared on the dorsa of the fingers of both hands. Towards the end of January, 1947, the rash began to spread to the dorsa of the hands, forearms, lower parts of the arms and, to a lesser degree, the face and neck.

Examination revealed a diffusely erythematous, scaling and lichenified eruption on the dorsa of the fingers and hands, the flexor aspects of the forearms, and the antecubital spaces, the eruption ending at the lower portion of the arms. The face and neck showed only a few fading lesions. The palms, feet and toes revealed no abnormalities.

The morphology of the eruption, its diffuseness and its distribution were features characteristic of eczematous contact dermatitis. This was further supported by the somewhat greater intensity of the eruption on the right upper limb (the patient was right-handed) and by the abrupt termination at the lower portion of the arms just below the point where the short sleeves of her uniform ended.

Among the substances which the patient had handled in the preceding three or four months were: codeine phosphate, morphine sulfate, tincture of green soap, ethyl alcohol, Brown mixture, Stoke's Expectorant, Pond's Cold Cream, and, very occasionally, Demerol hydrochloride. In addition, she had been injecting nightly about twenty-five tuberculous patients with a solution of streptomycin and, at the conclusion of this procedure, she had cleaned out all the syringes containing this substance. About ten days after she began to inject streptomycin solution, an eruption was noted on the fingers of the hands, with the clinical course as already described.

The patient was advised to stay away from work until the precise cause could be determined. This she refused to do for sundry reasons. However, she did take a short vacation of four days, and, on return to work, she used rubber gloves whenever streptomycin solution was handled. When she returned for patch testing about a week later, the eruption had almost completely disappeared.

Patch tests were applied for forty-eight hours in the following concentrations: codeine phosphate, morphine sulfate and Novocaine, each 1 per cent; Demerol hydrochloride, 2.5 per cent; streptomycin hydrochloride, 10 per cent; ethyl alcohol, 95 per cent; and Brown mixture, Stoke's Expectorant, Pond's Cold Cream and tincture of green soap, each undiluted. All the patch tests were negative, except for streptomycin hydrochloride, which showed a broadly erythematous, edematous and slightly papular reaction (graded about 2 plus), and Demerol hydrochloride, which elicited an erythematous and edematous response (graded 1-2 plus). The sites of these positive responses (the streptomycin and Demerol patches were adjacent to one

<sup>1</sup>From the Department of Dermatology, the Montefiore Hospital for Chronic Diseases.

<sup>‡</sup>This statement was true at the time we submitted this article for publication. Since then, a number of instances of streptomycin eczematous contact dermatitis have been reported by other observers.

another) had caused severe itching some ten to twelve hours after the patches were applied, the itching being sufficiently intense to awaken the patient from sleep.

In order, further, to show the specificity of these reactions, six control subjects were patch-tested with streptomycin and Demerol in the same concentrations. The results were negative. This evidence indicated, therefore, that the concentrations used were not primarily irritating to skin and that the positive responses in our patient were based on specific hypersensitiveness to these substances.

Since positive reactions were obtained with both streptomycin and Demerol, the question arose of whether the eruption was caused by one or both substances. The patient stated that she had handled Demerol very infrequently, the last date of contact being at least two weeks before the rash spread to the forearms, arms, face and neck. Contrariwise, the lesions had first appeared about ten days after she came into active and prolonged contact with streptomycin, and, with continued handling of the substance, the cutaneous lesions became more intense. As soon as the patient stopped handling streptomycin and also used rubber gloves, the eruption began to improve.

During the following month the patient again handled streptomycin solution. Although rubber gloves were continuously used, she was not careful in the way she carried out her duties. The eruption was much improved, but there were periods of mild intensification. Owing to an accident, she was forced to quit work for two weeks, and during this time the cutaneous lesions disappeared completely. On return to work, the eruption with its attendant severe itching recurred in a few days on the forearms, between the fingers and on the face. During this period she had handled *only* streptomycin solution. She admitted that she was careless in the use of the rubber gloves; for example, she had worn torn rubber gloves on several occasions. Moreover, it was a common occurrence for the patient to be splashed by the streptomycin solution while injecting it, and this had occurred on the exposed parts of the upper limbs as well as on the face.

Physical examination a few days after the eruption recurred disclosed diffuse, lichenified eczematous patches on the flexor surfaces of the forearms, with similar but more intense involvement of the antecubital spaces. There were similar eczematous areas of moister character in all the interdigital webs and along several fingers of each hand. There was also a mild scaly eczematous area, the size of a nickel coin, on the right side of the face near the lips. We wish to stress the point that during this period of recurrence, the patient had not handled Demerol hydrochloride, this duty having been taken over by another nurse.

Since the solution of streptomycin hydrochloride that had been used for the preceding patch tests was impure or relatively impure, the problem at this point was to determine whether the eczematous contact dermatitis was caused by streptomycin itself or by some impurity in the preparation. For this purpose we obtained a specimen of pure streptomycin in the form of a double salt (white, *crystalline* substance).\*

Patch tests with this pure streptomycin, in concentration of 10, 5 and 2 per cent solutions, showed the following results in twenty-four hours: 10 per cent, a widely diffused, erythematopapular reaction (graded 2 plus); 5 per cent, a more localized erythematous and edematous response (graded 1-2 plus); and 2 per cent, a mild erythema (graded plus-minus). It may be noted that the patient complained of severe itching in the patch test area, the sensation being localized definitely at the site of 10 per cent streptomycin solution. On the next day the reactions were more intense and ranged from 2-3 plus for the most concentrated solution to 1-2 plus for the least concentrated solution of streptomycin. Ten control subjects were patch-tested with these concentrations of streptomycin solution, the results being uniformly negative.

\*Streptomycin calcium chloride complex, Lot No. 7F1543, was supplied by the Medical Division of Merck and Co., Inc., and assays 759 units per milligram.

## DISCUSSION

Although the clinical data in the first attack of eczematous contact dermatitis favored definitely streptomycin as the cause of the eruption, the occurrence of a positive patch test with Demerol militated against drawing an absolute conclusion. However, the subsequent course established beyond any doubt that the eczematous contact dermatitis was caused by streptomycin.

Throughout the history of eczematous contact dermatitis, particularly since the nineteenth century, there has been a tendency to implicate impurities as the cause of such eruptions. In practically all instances this idea has not been substantiated by subsequent events. In the case which we have recorded, the same theory of impurities in the streptomycin might have been reasonably entertained, but patch test studies with a specimen of pure streptomycin showed definitely that the eczematous contact dermatitis was caused by streptomycin itself or, possibly, by its break-down products.

Streptomycin has been characterized chemically as a complex substance ( $C_{21}H_{39}N_7O_{12}$ ), composed of an amine-substituted disaccharide (streptobiosamine) that is linked to a 1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane (streptidine).<sup>2</sup> The streptidine portion of the molecule can be split off by acid hydrolysis.<sup>2</sup> If the sensitization to streptomycin should prove to be due to the whole molecule, this would provide the first example, as far as we know, of *eczematous contact dermatitis caused by a chemical containing a sugar radical*. It is of course possible that streptomycin is split by enzymatic action in the skin to liberate streptidine and streptobiosamine. If this should occur, streptidine would be more likely, in our opinion, to be the offending agent for two reasons: (1) eczematous contact dermatitis due to sugar molecules *per se* is unknown† and is most unlikely to occur with such substances, although we realize that the disaccharide streptobiosamine contains a substituted amine group; (2) the streptidine molecule contains two guanidine groups, and certain guanidine derivatives are known to cause eczematous contact dermatitis.

The chemical data thus far reported would seem to negate the possibility of a group or cross-reaction between streptomycin (or any possible break-down product) and Demerol, since in the former the chemical structure is that of a diguanidino-cyclohexane-disaccharide, whereas, in the latter the structure is that of a substituted piperidine molecule. These compounds seem to be too far apart chemically to postulate a cross-reaction. It appears more probable that our patient had two independent sensitizations.

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†The so-called sugar itch, which has been known since the early part of the nineteenth century and before, is a heterogeneous concept. Cases falling within this category have not been shown to be based on the mechanism of sensitization to the sugar molecule.

## SUMMARY AND CONCLUSIONS

We are reporting what seems to be the first instance<sup>‡</sup> of eczematous contact dermatitis due to streptomycin. Data are given to show that this substance in a pure form is capable of inducing this type of sensitization. If this type of sensitization is caused by the whole molecule, this would provide the first example of eczematous contact dermatitis due to a substance containing a sugar radical. It is possible, however, that the sensitization is due not to the disaccharide portion of the molecule (streptobiosamine) but rather to the streptidine portion of the molecule (diguanydino-tetrahydroxycyclohexane). This would presuppose the possibility that streptomycin can be split into these two major components by an enzymatic action on the part of the skin.

Nurses and others who handle streptomycin should use rubber gloves as a precaution and should avoid prolonged contact with this substance on the skin.

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<sup>‡</sup>This statement was true at the time we submitted this article for publication. Since then, a number of instances of streptomycin eczematous contact dermatitis have been reported by other observers.

## TREATMENT OF ALLERGIC AND OTHER DERMATOSES WITH PYRIBENZAMINE HYDROCHLORIDE

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# BROMOTHEN AND CHLORTHEN—5-BROM-2-THENYL AND 5-CHLOR-2-THENYL DERIVATIVES OF THE ETHYLENEDIAMINE GROUP

## Preliminary Report

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TO solve the riddle of treating allergic manifestations, the approach has been to tackle the allergen-reagin reaction. Most research is based on the histamine theory. The development of antihistaminics followed. Benadryl and Pyribenzamine have contributed much to palliative relief of allergic symptoms, but each has an extremely high incidence of side effects which are objectionable.

Litchfield and his co-workers<sup>1</sup> at the Stamford Research Laboratories have halogenized the ethylenediamine group (N, N-dimethyl-N'-2-pyridyl-ethylenediamine). They claim that this compound is much less toxic and much more effective than Pyribenzamine.

These compounds for convenience were labeled Bromothen\* and Chlorothen†. It was of interest to try these compounds to determine if the incidence of side effects (especially dizziness, drowsiness, tiredness) could be markedly reduced or eliminated. Therefore, twenty-six patients were chosen who had experienced these side effects from Benadryl and Pyribenzamine. These patients had urticaria and allergic rhinitis, and although they obtained relief, they could not continue therapy because of the uncomfortable side effects. Of this group, eighteen patients were given Chlorothen and eight were given Bromothen. All experienced relief of symptoms within fifteen minutes to half an hour after taking 50 milligrams. None had any side effects whatsoever. The patients were put on 50 milligrams three times daily. Six patients had adequate relief from symptoms after one day's use. The rest had to continue for two or more days (up to six) to have their relief prolonged.

Since the number of patients was small (only twenty-six), a larger group was given these compounds. Twenty-five additional patients who had never had either Benadryl nor Pyribenzamine were given Chlorothen and twenty-two were given Bromothen. The symptoms complained of were pruritis, rhinitis, urticaria, eczema, coughing and wheezing. So far none have experienced any side effects. Relief of symptoms was obtained as expected. The group is being enlarged to include more in number and more in varied allergic manifestations. Thus, material will be available for more detailed analysis to be reported at a later date.

This is in the nature of a preliminary report. This is not intended to

*(Continued on Page 441)*

Bromothen and Chlorothen supplied through courtesy of Lederle Laboratories.

\* 5-brom-2-thenyl-N, N-dimethyl-N'-2-pyridyl-ethylenediamine.

† 5-chlor-2-thenyl-N, N-dimethyl-N'-2-pyridyl-ethylenediamine.

# Editorial

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*The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.*

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## REACTIONS AND THEIR SIGNIFICANCE

Scientific papers are sometimes more important for what is incidental than for the original thesis. In the studies conducted by Cowan and Diehl, at the request of the Commission of Influenza of the Office of the Surgeon General, 666 students of the University of Minnesota were used as subjects. Of these, 346 received 1 c.c. of standard influenza A and B virus vaccine. A control group of 320 students was given 1 c.c. of physiological saline.

The severity of the colds seemed equal in both groups, their numbers being 2.9 colds for students who were vaccinated as compared to three for the controls. The complications were 19.8 per cent for the vaccinated and 21.0 per cent for the controls. Infirmary care was necessary for 1.6 per cent of the vaccinated students and 2.9 per cent for the controls.

The incidental finding, however, is of great importance to every worker in the field of injection therapy. Since none of the students knew the nature of the material injected, the study was an excellent test as to whether the material caused the reactions. In the vaccinated group, reactions were reported in 83.8 per cent of the students. But, in the unvaccinated group, the students receiving 1 c.c. of sterile physiological saline reported reactions totalling 22 per cent, more than one in five.

If the injection of 1 c.c. of physiological saline can cause reactions in more than one-fifth of the subjects, the effect of suggestion and of psychotherapy in injection treatment cannot be underestimated, if it can be estimated at all.

## THE ALLERGEN OF HOUSE DUST

Although house dust is one of the most frequently used antigens in the therapy of the allergic patient, there is very little that has been determined quantitatively of the nature of the active constituent. A start in this direction has been made by Rimington, Stillwell and Maunsell. In the *British Journal of Experimental Pathology* (28:309, 1948), it is shown that a purified antigen which gives positive reactions in sensitive individuals can be prepared from house dust. This contains about 25 per cent hexose and 2.5 per cent nitrogen. Acid hydrolysis liberates a reducing sugar, probably galactose, and some simple amino acids. Tyroine and histidine are absent. Milder acid hydrolysis liberates 80 per cent of the carbohydrates but no

amino acids. An antigen remains with undiminished activity containing 12 per cent hexose and 10 per cent nitrogen. It is of interest that the antigen before or after the mild hydrolysis shows two main components electrophoretically: one mobile and colored, and the other immobile and colorless. These are similar in composition, to a certain extent, and also in antigenic potency. It is of interest that these pioneer electrophoresis experiments with dust show similar results to those which have previously been reported in detail with the electrophoretic fractionation of the pollen antigens. Thus, in all of the pollen antigens investigated thus far, there are essentially immobile, colorless antigens with a number of pigments colored and mobile. Further investigations of this type with purified allergens, in all likelihood, will provide a better immunochemical basis for the behavior of the sensitized individual.

The same authors (Stillwell, Rimington and Maunsell) in a second paper show that a general similarity exists between polysaccharide products derived from molds and preparation of the house dust antigen. They are all, like the main pollen allergens, of polypeptide structure associated with a polysaccharide complex. The pollen allergens have been designated as "protoproteins," that is, intermediate in size between the polypeptide molecule and protein. We can look forward to further information on the nature of these dust allergens when their molecular weights are determined in the ultracentrifuge. By these modern techniques, much of the obscurity connected with pollen allergens and a good deal of the confusion will be ultimately eliminated.

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### BROMOTHEN AND CHLORTHEN

*(Continued from Page 439)*

be a study to draw adequate conclusions, but the results were such as to warrant the formation of a larger group with other allergic manifestations for further study. A report on the results obtained will be made on a sufficiently larger series of cases to draw adequate conclusions.

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# Progress in Allergy

## ALLERGIC SKIN DISEASES

### Review of Recent Literature

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#### ATOPIC DERMATITIS (Neurodermatitis Disseminata)

Analyzing our present and past concepts of atopic dermatitis and summing up what is known concerning its immunologic background, A. Rostenberg, Jr.,<sup>4</sup> states the following facts:

1. Many individuals give multiple positive immediate whealing reactions to protein substances.

2. These substances do not seem to influence the course of the dermatitis; exposure to them usually does not cause an exacerbation, and their elimination does not lead to improvement.

3. Individuals with atopic dermatitis yield positive patch test reactions to protein or to heavy metals.

The nature of these reactions is unknown, but they signify some sort of dermo-epidermal sensitivity other than the wheal type. In order to weld these facts into a single immunologic theory which is consistent with the clinical observations, Rostenberg suggests the following hypothesis of a dual hypersensitivity:

1. Individuals with atopic dermatitis have an immediate wheal-type sensitivity. Consequently they will have an antigen-antibody reaction. The effects of such a reaction are alteration of capillary permeability and release of histamine and probably other substances.

2. A dermo-epidermal sensitivity exists in these individuals either to the same or different allergens. However, these allergens cannot get to the epidermis or cannot make their effects manifest in the epidermis until the "capillary door" is opened to them by the alterations in capillary permeability, which results from the wheal-type of reaction.

Rostenberg has made a worth-while attempt to correlate the immunologic background and clinical observations in atopic dermatitis. The situation is still rather confusing; there are too many unknown factors and contradictory opinions. The causative significance of the "atopic" allergens in atopic dermatitis is not yet settled; their role had been overemphasized previously; at present the pendulum seems to swing too much in the other direction.

There are cases of atopic dermatitis that can be reproduced by exposure to the allergen which produced an immediate whealing reaction. Rostenberg's vascular theory explains perhaps why this seems more often the case in localized atopic dermatitis when the allergen penetrates the skin from without (Hill's atopic dermatitis by contact). I may mention in this respect some cases of atopic dermatitis from pollens; those cases of "milker's eczema" that are due to cattle sensitivity, and instances of "baker's eczema," which are accompanied by whealing reactions to wheat.\* Of eight cases of baker's eczema among 653 bakers in Finland, Kilpinen<sup>5</sup> reported four that gave positive whealing reactions to wheat and also to rye and barley. There was no reaction to the flour-improving substances.

Most observers will probably agree with Rostenberg that the pathological and clinical discrepancy between a chronic atopic dermatitis and a chronic contact eczematous dermatitis is really not very great. However, these instances of chronic dermatitis are probably of a more complex and complicated nature. Atopic dermatitis has been viewed too much from the atopic angle, and contact dermatitis too much as a mere eczematoid sensitivity. There is little known about their in-

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\*Baker's eczema may be caused by a variety of factors. Some of the cases apparently are contact dermatitis with hypersensitivity to the substances added to improve the flour, especially persulfates.

terrelationship. Two competent observers present opposite views. Tolmach's<sup>7</sup> impression is that the atopic individual is not more easily sensitized in industry than the so-called normal people. In Downing's<sup>2</sup> experience, however, atopic individuals should not work where they will contact sensitizing chemicals.

According to Rostenberg, in atopic dermatitis there is an epidermo-dermal sensitization other than the wheal type. What the allergens may be is still an open question. Simon's work on the role of human dander is well known. Recently<sup>6</sup> he found that the allergen of human dander is also present in skin of the general body surface, although extracts from the scalp dander were much more active allergenically. The identity of the allergenic principle of dander and normal skin was proven by passive transfer experiments and neutralization of reagins.

Weedon<sup>8</sup> believes that common intestinal fungi may be the source of allergens in certain severe cases of chronic atopic dermatitis. The stool specimens of ten individuals examined showed heavy growths of yeastlike fungi—*Candida albicans* occurring once, *Candida tropicalis* once, *Geotrichum* four times—and other yeasts not yet identified, as well as heavy growths of various molds. Eight patients were treated with fungicides and showed great improvement. Potassium iodide by mouth effected striking improvement temporarily in two patients, but in one of these the initial dose was followed by a severe temporary exacerbation of the disease. Seven patients were treated by immersion with phenacyl iodide 1:1,000 over the thighs and cautiously over the lesions. None of these showed exacerbation, and all steadily improved to total or near total freedom from eczema. In most cases the number of yeast colonies in consecutive stools decreased with treatment.

In this connection one is reminded of Guiz-Moreno's<sup>5</sup> eczematoid monilid. From the clinical description his cases seem to fit in with localized atopic dermatitis of the neck and eyelids; the author, however, believes this condition is not atopic, as it was not possible to prove the presence of reagins. The eczematous syndrome usually affects women and is localized on the eyelids, lips, and neck, where it appears as a dry, scaly and pruritic dermatitis, usually in the spring and fall. Patients show both immediate and delayed reactions to intradermal tests with a potent extract of *C. albicans*. Guiz-Moreno considers the condition a special and frequent manifestation of a monilid. There is absence of mycotic infection at the site of the rash; positive delayed reactions to an extract of *C. albicans* indicate an "infectious" or "tuberculin-type" allergy; exacerbation follows the injection of an excessive quantity of the extract; therapeutic administration of the extract subcutaneously produces complete cures; and an intestinal focus of *C. albicans* is demonstrated. In treating these patients with an extract of *C. albicans*, the curative dose varies widely, from 3 to 1,000 Coca units. Often the curative dose is very close to the reaction-producing dose.

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#### INFANTILE ECZEMA

According to Ratner<sup>3</sup> best results in the management of eczema in children are obtained if the condition is viewed from the standpoint of diet, environment, psychosomatic and constitutional phases, in conjunction with local dermal therapy.

Infantile eczema is the prevailing allergic condition in infancy and is the earliest of all the allergic syndromes. In Ratner's experience the average age of onset was one and nine-tenths months. Positive allergic skin reactions were obtained in 85 per cent of the patients under one year of age. All of these positive reactors were sensitive to foods, but only 41 per cent of them reacted to foods alone. Fifty-nine per cent reacted to a combination of foods, inhalants and contactants. Ratner uses the following procedures prior to skin testing. The child is placed on a diet of allergenically denatured foods such as evaporated milk, pabulum, pabena, thoroughly cooked cereals and vegetables, thoroughly boiled meats, hard boiled eggs and stewed fruits. A dustproof environment is recommended, animals should be removed.

For local treatment Ratner lists the commonly used antieczematic measures. For secondarily infected, wet, oozing skin a 2 to 4 per cent aqueous solution of gentian violet at times proves the most gratifying compound. Phenobarbital in small doses and acetyl salicylic acid in 3 to 5 grain doses, or their combination, are the sedatives of choice. The antihistaminic drugs allayed the pruritus only to some extent in Ratner's experience, whereas Wolpe<sup>8</sup> found that Pyribenzamine gave great relief from itching in a large number of cases.

Wolpe<sup>8</sup> presents in detail the management of infantile eczema as practiced at the Los Angeles County Hospital. The reader is referred to the original. In contradistinction to Ratner<sup>3</sup> who does not differentiate between atopic dermatitis and contact dermatitis in children, Wolpe follows a modification of the Hill-Sulzberger classification of infantile eczema. Wolpe deplores the attitude of many clinicians that eczema may be ignored because "it will sooner or later clear." By proper treatment much misery on the part of both infant and parent can be avoided. It has been Wolpe's experience that itching persists for some time after the skin has completely cleared. He believes that if restraints are discontinued less than two to three months after clearing, traumatic relighting of the eczema is probable. The allergic management is carried out by placing the child on a very restricted diet, and putting it in an environment as dust-free as possible. Skin testing is not mentioned in his paper. For various reasons, and because Wolpe feels that there is a "growth factor" in milk, he has attempted to maintain the patient on milk for at least one week. In another study, Wolpe<sup>6</sup> found, however, that babies fed milk substitutes reach clinical relief faster than those fed on a milk diet. Wolpe<sup>7</sup> also observed that nutritional crises, characterized by edema, dehydration, apathy, listlessness, anorexia, profuse diarrhea, or actual prostration, occurred in infants suffering from severe generalized eczema. Routine weekly hemoglobin and albumin-globulin determinations revealed a startling incidence of hypoproteinemia. This was recognized as being frequently present with deficient food intake, such as in presence of elimination diets and/or failure of complete absorption, and with excessive food loss, such as with allergic diarrhea. In a series of fifty-four cases of infantile eczema, 26 per cent revealed a protein deficiency. In these the globulin fraction showed a greater percentage of deficiency from normal than the albumin fraction.

The therapy consisted of (1) liver extract 0.5 c.c. (7.5 units) to six months and 1.0 c.c. over six months of age, intramuscularly twice weekly; (2) vitamin B complex 1.0 c.c., intramuscularly twice weekly; (3) intravenous plasma; (4) intravenous blood alternated with plasma when hemoglobin value was low; (5) one tablespoon twice daily of hydrolyzed amino-acid mixtures; (6) dietary elimination.

One of the most dreaded complications of infantile eczema is the so-called Kaposi's varicelliform eruption. Cases are reported by Barker and Hallinger,<sup>1</sup> Lynch and Steves<sup>2</sup> and Ruchman, Welsh and Dodd.<sup>5</sup> According to Ruchman et al, Kaposi described a syndrome, occurring in children who had a pre-existing atopic dermatitis, which was characterized by recurrent crops of lesions that went through stages of vesiculation, umbilication, desiccation and rupture; when these lesions healed only the signs of the original atopic dermatitis persisted. Juliusberg described a fatal case in which there were similar lesions to those described by Kaposi under the title of "pustulosis acuta varioliformis." An eruption similar to the one described by Kaposi has been noted in individuals exposed to recently vaccinated members of the family, or who have themselves recently been vaccinated, and in many of these cases the vaccine virus was recovered or the Guarnieri bodies were demonstrated. Recently the virus of herpes simplex has been isolated from several patients presenting this syndrome, and it is now thought that there are at least two causes for these similar eruptions—one caused by the virus of vaccinia and known as eczema vaccinatum, and the other caused by the virus of herpes simplex and known as Kaposi's varicelliform eruption. There have been ninety-six cases of this condition reported in the literature, and of these, seventy-five occurred in children and only twenty-one in adults. The authors report four additional cases, three occurring in adults and one in an infant aged fourteen months. All four patients gave a history of a definite exposure to the virus of herpes simplex from five to ten days prior to the onset of their eruption, and none knew of any exposure to the virus of vaccinia. Strains of herpes simplex virus were isolated from the cutaneous lesions of all four patients. The antibody titre increased during convalescence in two of the adult patients, but in the one fatal case, which occurred in an adult, there were no antibodies during the acute stage of the eruption.

Riley and Callaway<sup>4</sup> feel that although similar clinical pictures appear in eczema vaccinatum and Kaposi's varicelliform eruption, there are sufficient differences to suggest the diagnosis without laboratory procedures. They point out that in eczema vaccinatum there is usually a history of vaccinia contact, while in Kaposi's varicel-

liform eruption there is a history of herpes simplex contact. In eczema vaccinatum the lesions go through typical stages of a vaccinia eruption, while in Kaposi's varicelliform eruption they may be similar in some cases, but they usually are typically herpetic, and frequently the grouping is characteristic of herpes simplex. Additional points of differentiation between these closely related conditions are tabulated. To definitely establish the diagnosis, virus studies are at times necessary. The authors report two cases of eczema vaccinatum in which there was a definite history of exposure to vaccinia, and in which virus studies were carried out.

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#### PSYCHOSOMATIC ASPECTS

Although psychologic influences may play some role in various eczemas, they are more important in atopic dermatitis. A study of the automatic nervous system in "atopic" individuals is presented by Cohen and Wolf.<sup>2</sup> The clinical observation of increased palmar sweating in disturbances of the autonomic nervous system has long been recognized. A significant increase in the incidence of intensive palmar sweating in anxiety has been demonstrated. Patients with allergic-respiratory disease, mostly bronchial asthma, manifested a statistically significant increase in the incidence of intense palmar sweating. Cohen and Wolf believe that clinically manifest allergic-respiratory disease in man is dependent on an inherent behavior pattern of the autonomic nervous system in addition to the immunologic factor of hypersensitivity. (Such a study might also be worth-while in regard to patients with atopic dermatitis.)

Woodhead<sup>10</sup> reports a psychologic study of a group of twenty-six children and young adults suffering from eczema, atopic dermatitis and papular urticaria. They had resisted regular treatment, but were cured by psychotherapy. Woodhead found often unconscious psychologic problems in the parents, affecting the child as well as psychologic difficulties of the child itself. The children are generally abnormally gifted, energetic, determined, aggressive and egotistical to the point of narcissism. In addition they are frightened and unsure because of great sensitivity. The healing of the skin disease runs parallel with the successful psychological treatment. There is a tendency to slight relapses during the treatment, when faced with difficult situations. The skin disorders are a reaction to an unfavorable environment or to a psychological shock. The author recommends an early and careful psychological treatment of the child and of the parents to avoid allergic reactions becoming permanent.

Schneider and Kesten<sup>7</sup> studied ten cases of what they call polymorphic itching dermatitis or polymorphic prurigo. This condition corresponds to that previously described under such various names as generalized erythroderma, distinctive exudative discoid and lichenoid chronic dermatosis, and allergic dermatitis simulating lymphoblastoma. According to these authors, this dermatologic syndrome, while difficult to define, has become recognized as a fairly distinct clinical entity. The etiology remains obscure, although a history of personal or family allergy is usual. Severe and uncontrollable itching, together with the prevalence of emotional disturbances, has been stressed in most of the previous studies. Hospital care and permanent residence in a sunny dry climate are beneficial. Psychosomatic studies of Schneider and Kesten's cases indicated an etiologic relationship between emotional conflict of the patients and their dermatitis. While in a state of marked anxiety and guilt related to a particular conflict, an individual develops a mild localized dermatitis that may be or may simulate one of the common dermatoses. This simple dermatitis may go over into a severely pruritic polymorphic recalcitrant dermatitis because of the concomitant effective disturbance of the autonomic control of the skin. Etiologically many factors are probably impli-

cated, of which the psyche is only one, but its paramount importance is indicated by the major position that psychotherapy occupies in successful treatment.

After some months' residence in the southwest away from unsatisfactory emotional environment, seven patients became free from this eruption. Of this group, five have remained in the southwestern states and are ostensibly cured. The other two patients returned to the east, one to her old surroundings, where she has had a recurrence of the eruption, the other to an emotionally satisfactory environment where he has remained well. The remaining three patients underwent a psychosomatic study. After therapy two of the three have remained well while living in their habitual environment. This study indicates that emotional conflict is of singular importance in the evolution of polymorphic prurigo and that psychotherapy is a major factor in its successful treatment.

According to Robertson,<sup>6</sup> patients with intractable dermatitis may sometimes be found to labor under a deep sense of grievance. Inquiry into the emotional difficulties associated with the onset of the dermatoses may cause an acute exacerbation. The technique of treatment should be directed toward extirpating a sense of injustice from the patient's emotional life.

Forman<sup>4</sup> used Evipan in the investigation of twenty military patients who presented recurrent and chronic dermatoses. Progress had been unaccountably delayed; in many cases symptoms and signs were exaggerated. Evipan was slowly given intravenously in a 1 per cent solution until the first stage of anesthesia was reached. Usually 0.4 gm. was sufficient. The patient was then questioned, and any answer that appeared of significance was pursued. If replies became guarded, or ceased, more Evipan was given until the patient was again relaxed and sleepy, resistance to questioning was removed, and the answers again given freely. There apparently was no period of amnesia following such procedure.

With suitable doses of the barbiturate, intellectual criticism and emotional control were removed. The patients had a feeling of confidence and a desire to communicate. Intimate questions were answered freely, and a surprising depth of mental processes and emotional content were revealed. The information gained during these procedures was used in subsequent discussions with the patient to further his understanding of the relationship between his difficulties or conflicts and his cutaneous disease.

The author's clinical diagnoses in these cases were lichenification, excoriated dermatitis, urticaria, pruritus, and dermatographism. Following Evipan, the cases were regrouped as anxiety state, purposive conflict, maternal attachment, depression, and paranoid. The author points out that a short "narcoanalysis" under Evipan cannot take the place of a careful personal history by a trained psychologist and of his evaluation of personality and the effects of mental trauma. Evipan narcosis offers a quick and probably reliable method of psychologic investigation, particularly if the services of a psychologist are not readily available.

Walsh and Kierland<sup>9</sup> treated fifteen patients with atopic dermatitis (generalized neurodermatitis) with psychotherapy. These patients had failed to respond satisfactorily to dermatologic treatment. Certain characteristic emotional patterns were noted, of which the authors consider the following the most prominent ones: "Suppressed hostility toward the mother or a mother figure was present in most. The skin was apparently utilized in these patients as a site for expressing strong unconscious conflicts relating to exhibitionistic tendencies and a frustrated desire for love and affection. The possibility exists that the mutilation of the skin by scratching and excoriation may have had the significance of self-punishment or partial suicide. This was thought to be related to guilt feelings resulting from hostility and death wishes toward the mother or mother figure in most if not all of the patients. The patient thus, in fact, made himself unlovely, which may correspond to his feeling that he was unworthy to be loved or even unlovable. There was a strong tendency in all of these patients toward the handling of strong emotion through suppression. In all of the patients whose dermatitis had begun in adult life, it had been preceded more or less immediately by a frustrating experience. In the five patients whose dermatologic reaction had begun in childhood, the emotional disorder appeared deeply rooted in the personality, and striking results from psychotherapy were not obtained. In three patients with marked depressive reactions, a series of electroshock treatments was also given, with one failure in a patient to whom effective psychotherapy could not be given because of language difficulty. With this one exception, improvement in the emotional disorder was paralleled by a complete or nearly complete clearing of the dermatologic reaction, and this improvement has endured during the period of observation in all patients whose dermatologic reaction had first appeared in adult life. Marked

improvement or disappearance of asthmatic symptoms concurrently occurred in the four patients in this group who had asthmatic syndromes."

According to Lewis and Cormia,<sup>5</sup> little progress has been made in the psychological interpretation and management of the cutaneous manifestations of psychosomatic disease. The psyche unconsciously selects any convenient locus minoris resistentiae for the cutaneous expression of internal conflict. Bodily emotions symbolically expressed by the skin include those of worry (picking), anxiety (pruritus and sweating), fear and anger (urticaria), guilt and shame (blushing and rosacea), hostility, masochism and eroticism (dermatitis factitia) and sexual pleasure (cutaneous masturbation).

Such devices may directly aid in avoiding unpleasant reality by producing disability or a socially acceptable sublimation of a conflict. According to the classification of Lewis and Cormia, lichen simplex chronicus (localized neurodermatitis) and acute neurodermatitis are always psychogenic, but often with additional etiologic factors as well. Pruritus, urticaria, and dyshidrosis of hands and feet are frequently, but not always, psychogenic. As dermatoses which combine psychogenic and other etiologic factors, the authors classify atopic dermatitis (disseminated neurodermatitis), contact dermatitis, and dermatitis medicamentosa. Lewis and Cormia attempt a symbolistic interpretation of the underlying conflicts in patients with psychosomatic dermatoses. These conflicts are expressed by the type of lesions as well as by the localization. Here are some examples relating to eczemas: Lichen simplex chronicus—long-standing worry and anxiety with makeshift adjustments. Acute exudative neurodermatitis of flush areas—severe anxiety, acute or prolonged unsolvable conflicts. Atopic dermatitis—prolonged social resentment, hostility, compensatory aggression. Urticaria—acute phobias with anxiety, hostility, and anger. Examples of expression of psychosomatic conflict by localization are given as follows: Head (rosacea, seborrheic dermatitis, eczematous ear)—social anxiety, stigmatization, guilt. Hands and feet (pompholyx)—dislike or fear of occupational duties. Ano-genital sphere—sexual or domestic disturbances, maladjustments or frustration in these spheres.

The psychosomatic study of a dermatosis embodies all that is best in routine dermatologic and psychiatric care. It involves tracing the psychic and physical growth of a patient through his life span and constructing a basic personality pattern.<sup>3</sup> Prolonged, painstaking therapy is required. Best results, in Lewis and Cormia's experience, were obtained when both psychical and psychic measures were included. The purely symptomatic approach did not correct the underlying problems. In these instances, relapse, development of another "neurodermatosis," or psychosomatic complaints involving other organs would result almost inevitably. With the combined methods, the results were decidedly good: 50 per cent of the group were cured or markedly improved. Lewis and Cormia's views are not generally accepted. Sulzberger and Baer<sup>8</sup> state that there is no proof that psychic or neurologic factors are regularly of major importance in the various eczemas. The Freudian approach to psychosomatic disorders is outrightly condemned and called "unscientific" by Campbell.<sup>1</sup> He agrees that "inter-reactive influences which exist between the emotional, intellectual, and other bodily functions and the soma in its entirety, and reality outside the body should be taken into consideration," but stresses that "the complexity of these relationships should not be relegated to a group of fanatics who have succumbed to the hypnotic technique executed by Freudians in the training of pupils and perpetuated by these trainees who have become and continue to become trainers of subsequent trainees, all of whom are under the spell of the systematized delusion of psychoanalysis."

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## PROGRESS IN ALLERGY

### CONTACT DERMATITIS

*Mechanism of Eczematous Sensitization.*—Landsteiner and Chase originally demonstrated in 1942 that cutaneous hypersensitiveness of picryl chloride may be transmitted passively to normal guinea pigs by intraperitoneal injection of cell suspensions obtained from experimentally produced peritoneal exudates in sensitized guinea pigs. Chase later showed that cells from the spleen and lymph glands are able to transmit this effect. Haxthausen<sup>13</sup> has confirmed these experiments using dinitrochlorobenzene and dioxanthogen. He further demonstrated that cell suspensions of the thymus may also be used successfully. Thus, confirmatory evidence is furnished that cellular elements, especially lymphocytes, are carriers of the hypersensitiveness in contact dermatitis. Haxthausen also attempted passive local transmission with fresh lymphocytes and with extracts of such lymphocytes. Negative results were obtained in both guinea pigs and humans; in the latter, cells from the blood as well as from excised lymph glands were used. Hence, it is still an open question how the active principle in the lymphocytes is transmitted to the skin and by what manner they convey their specific capacity for reaction.

A working theory to explain the physiologic process of eczematous sensitization has been proposed by Rostenberg.<sup>31</sup> His theory embraces the work of many investigators, including himself. It is known that many substances are capable of causing an eczematous sensitization; yet experimentally only a relatively few compounds are regarded as reliable agents for reproducing this phenomenon with any degree of consistency. The explanation possibly lies in the persons rather than in the chemicals. There may be some peculiar genetic predisposition, or there may have been some special favoring circumstance, such as inflammation, at the time the allergen was encountered. It is also generally realized that the easiest route by which eczematous sensitization can be achieved is by application of the material directly to the skin, but this is not necessarily the only route. Rostenberg's theory holds that the allergen when applied to the epidermocutis reacts to form a new

This substance appears to be a protein conjugated with the simple chemical or with some derivative of it. The compound allergen next leaves the skin primarily via lymphatic channels.<sup>30</sup> Six to nine days later the entire epidermis, as a rule, becomes sensitized. Practically nothing is known regarding the site of development of this hypersensitivity although this may occur in the regional lymph nodes. The antibodies formed are contained within the lymphocytes and possibly other cells. There are no humoral antibodies contained in centrifugal serum. However, if cells are involved in the passive transfer, the antigen-antibody mechanism may be demonstrated (Landsteiner, Chase, and Haxthausen). According to Rostenberg, two points about eczematous sensitization especially require elucidation. In the first place, why is the application of the allergen to the epidermocutis a superior route for the engendering of the sensitization; and secondly, what is the nature of the antibody formed and wherein does it differ from other more easily demonstrable antibodies? In regard to the first question, Rostenberg believes that the allergen has to be deposited at a site relatively rich in macrophages. The true cutis is such a site. He further believes that the ability to sensitize is increased if the compound allergen is insoluble (particulate). In response to the second question, Rostenberg emphasizes that the salient feature of the eczematous antibody is that it does not exist free in the circulation. It has a cellular affinity, probably as a result of the antigen incorporating a portion of the body's protein into its being, thereby increasing the specificity of the resulting antibody. A simple chemical then introduced to this sensitized tissue completes the eczematous reaction. From the foregoing, it is apparent there is still much work to be done on the physiologic mechanism of eczematous sensitization.

It has been shown by Miller<sup>22</sup> that contact eczematous dermatitis presents a definite and characteristic histologic picture by which it can be identified. The outstanding features of this disease are of two types, one resulting in necrosis of the epidermis and the other producing vesicular formation due to edematous degeneration of the prickle cells. The cutis shows congestion of the superficial blood vessels with a perivascular banal type of inflammatory exudate. Miller enumerated the essential points in the histologic differentiation of this disease from other members of the group of eczematous dermatoses.

Sulzberger<sup>39</sup> has expressed a preference for the name "allergic contact-type eczematous dermatitis" and has clearly defined and justified each word of his proposed designation for this type of dermatitis. He pointed out that aside from local dermatologic management, there is no specific therapy other than discovery and elimination or reduction of the causative allergens. Sutton, Jr.,<sup>41</sup> has outlined his technique of eliminating and identifying an unknown irritant. All possible causes are removed and later reintroduced into the environment one by one. A



flare-up incriminates the substance last introduced. The author claims originality from this point of view. Patch tests are not undertaken, and guess work is eliminated.

Wodehouse<sup>19</sup> devised a system of measuring and recording the intensity of skin reactions. A "cutaneous reaction unit" is defined as a wheal 1 mm. in diameter surrounded by an erythema 1 mm. in excess of the wheal, or 2 mm. in over-all diameter. Intensities or reaction units may then be expressed by multiplying the wheal diameter by the excess of the erythema diameter over that of the wheal in millimeters or  $n = w(e - w)$ .

*Eczematous Sensitization to the Antibiotics.*—Eczematous sensitization may result from contact with either penicillin or streptomycin and constitutes an actual occupational hazard to those handling and administering these drugs. MacInnis<sup>20</sup> has reviewed the literature on allergic reactions from handling penicillin and has determined the incidence of the various possible reactions and their locations. Itching of the skin of the face, neck and body (indirect contact) is the most frequent response. She reported the histories of two nurses who developed symptoms other than dermatitis from handling penicillin. The first nurse had nasal congestion, itching, and whealing. The second had photophobia associated with conjunctivitis and edema of the eyelids. Hoffman<sup>21</sup> found that 40 per cent of his cases developed a contact dermatitis when penicillin wet dressings were used for more than four or five consecutive days.

An increasing number of reports in the literature testify to the fact that streptomycin is likewise a potent cutaneous sensitizer. Strauss and Warring<sup>22,23</sup> were among the first to call attention to this fact. They reported six cases of epidermal sensitization from streptomycin occurring among twelve nurses handling the drug. Four of these nurses presented a dermatitis; the other two were found to be sensitized on patch testing. Dermatitis developed after an interval of from one to three and one-half months after beginning exposure to the drug. These authors had little doubt that streptomycin itself and not an impurity was responsible for the sensitization inasmuch as the six subjects all reacted to two different lots of the drug and also to a preparation which was 98 per cent pure. Six cases of sensitization developing in twelve nurses indicated that the index of epidermal sensitization to streptomycin was high. Two additional cases of epidermal sensitization developing after prolonged exposure through handling of streptomycin were reported from another source.<sup>24</sup> Canizares and Shatin<sup>5</sup> reported three additional cases of contact dermatitis from streptomycin in nurses handling the drug, making solutions, and giving injections. Patch tests and intradermal tests with streptomycin were positive. The Report of the Council on Pharmacy and Chemistry<sup>6</sup> reported "more than a dozen instances" of contact dermatitis from the drug. Rauchwerger et al<sup>25</sup> reported six more cases among nurses. All were characterized by an initial erythema followed by a pruritus and a papulovesicular eruption. The pruritus was the most distressing symptom. In two cases there was actual denuding of the skin over the terminal phalanges of the thumb and index fingers of both hands, indicative of the more frequent exposure of these parts in handling syringes and needles. Five of the six subjects showed involvement of the periorbital areas, most probably a result of autoinoculation. These nurses were in intermittent contact with the drug for periods varying from eight to eighteen months, again demonstrating that sensitization develops only after prolonged exposure. Prophylactic measures for nurses administering the drug include the wearing of rubber gloves and frequent washing of the hands. Steam emanating from sterilizers in which needles and syringes have been sterilized should be avoided as this may furnish one source of exposure.<sup>26</sup>

Senturia and Broh-Kahn<sup>32</sup> treated fifty patients with otitis externa with an ointment containing from 250 micrograms to 5 mg. of streptomycin per gram of ointment base. No mention was made of any sensitization reactions.

*Antihistaminics in Contact Dermatitis.*—The question of the value of antihistaminics in the therapy of contact dermatitis is still unsettled.<sup>2,21,24,28</sup> There is a question whether the effect in this condition is due to the antihistaminic action of these drugs. According to Dreisbach,<sup>8</sup> central depression by these drugs or their local anesthetic action may be responsible for the subjective relief obtained. The controversy is discussed in the chapter on antihistaminics.

*Formaldehyde-treated Starch.*—Talcum powder, when introduced into traumatized tissue, is capable of producing a chronic inflammation of the granulomatous type. The risk involved in using talcum powder on surgeons' gloves is apparent and has



stimulated a search for a substitute powder. Potassium bitartrate was suggested and used, but it is not without shortcomings. More recently a formaldehyde-treated corn starch preparation has been introduced. The formaldehyde apparently changes the molecular structure of the starch, removing its gelatinizing properties, so that even when steamed or boiled it still remains a free-flowing dusting powder. When introduced into body tissues it is absorbed and does not produce a foreign body granuloma. Gottschalk<sup>12</sup> undertook an investigation to determine whether this substance was primarily irritating or capable of producing a contact dermatitis. Two hundred and eight volunteers were patch-tested with the material. There were no positive reactions. Ten to fourteen days later the entire group was retested. One positive reaction was obtained. This subject was shown to have a formaldehyde sensitivity. However, on a third test with formaldehyde-treated starch no reaction was noted. Eiseman et al<sup>9</sup> are of the opinion that the formaldehyde starch is somewhat unstable and, on aging, seems to split up, liberating free aldehyde which may act as an irritant to the hands of the surgeon. They reported that one of their resident surgeons developed an irritation of the hands from an aldehyde-treated starch.

Mumford and Auckland<sup>23</sup> reported the case of a patient who showed recurrent congestion, erythema, and irritation on the cheeks and eyelids over a two-year period. Investigation revealed that the odor of burnt coal gas was discernible at the patient's place of employment, and that attacks invariably occurred within twelve hours after a day when the odor was strong. This patient showed a positive patch reaction to formaldehyde. It was concluded that minute traces of aldehydes in the burnt coal gas were responsible for his illness.

*Soap and Cosmetics.*—Lane and Blank<sup>17</sup> have shown that among the sodium salts of the fatty acids commonly contained in soaps (lauric, myristic, palmitic, and oleic), only sodium stearate and sodium palmitate elicit a relatively low percentage of positive reactions on patch tests. Stearic acid and palmitic acid usually produce no reaction on patch test in the presence of a buffer solution of pH 9. They also demonstrated that highly sulfated oleic acid (sulfato-octodecanoic acid) is usually innocuous on patch testing. It is, therefore, not surprising that these investigators found that a solid lathering cake detergent made primarily from stearic, palmitic, and sulfato-octodecanoic acids and containing little or no lauric acid or oleic acid was non-irritating to the skin both by patch tests and by clinical investigations. Such a product is commercially available as Dermolate.

Sharlit<sup>23</sup> has pointed out that the acid character of the cutaneous surface has led to the opinion that the regular application of alkaline substances to the skin may be responsible for the production of a dermatitis or the maintenance of it. Soap has been so incriminated, but the author is not convinced that the alkalinity *per se* of toilet soap is dangerous. In proof of his point, Sharlit demonstrated that eighteen random commercial face powders all gave alkaline reactions. This appears to be ample evidence, in view of the widespread use of face powder, that the skin tolerates habitual exposure to moderate degrees of alkalinity.

The problem of eczematous sensitization to hair dye is important because of the increasing use of these agents. The so-called penetrating dyes obtained from coal tar are the most efficient, but they are also most likely to produce irritation. Lawrence<sup>18</sup> has reported six cases of dermatitis following the use of paratoluylenediamine hair dye. The eruption was usually noted after repeated exposure. Other related dyes containing para- or meta-phenylenediamine are also commonly used. In the general population idiosyncrasy toward these chemicals is about 4 per cent.<sup>1</sup> Dermatitis from cold wave solutions is well known. A discussion of the chemicals and gums used in cold waving, along with a description of the procedure, has recently been published again.<sup>26</sup>

Zakon et al<sup>27</sup> believes that cheilitis from lipstick is more frequent than is generally realized. These authors claim that the bromfluorescein dyes which are used in lipsticks are more frequently the cause of cheilitis in women than any other factor. Lipstick dermatitis is characterized by swelling and edema of both lips. Scaling, fissuring, superficial erosions, and occasionally small grouped vesicles may be present. In thirty-two cases of lipstick dermatitis, treatment consisted simply of eliminating lipstick containing bromfluorescein dyes.

*Cross-Sensitization.*—Since R. L. Mayer's original work on cross-sensitization there have been many contributions to the subject. A brief summary is herewith given of those which appeared within the scope of this review. One of Lawrence's patients with a dermatitis due to paratoluylenediamine hair dye reacted to patch tests with that substance and also showed a severe reaction to paraphenylenediamine.<sup>18</sup> In

thirteen cases of allergic eczematous contact-type dermatitis due to nylon stockings, Dokkevitch and Baer<sup>7</sup> showed that azo dyes were responsible, and they were able to demonstrate a cross-sensitization with paraphenylenediamine. Likewise in five subjects with known sensitivity to paraphenylenediamine, they were able to demonstrate cross-hypersensitivity to the azo dyes of the nylon stockings in three. Cornbleet<sup>5</sup> was not able to demonstrate any cross-sensitization to a number of compounds partially related to BAL. However, it is possible that substances with chemical structures more closely allied to the BAL molecule would have yielded more information.

The essential allergen in oil of citronella was found by Keil<sup>15</sup> to be citronellal, an aliphatic aldehyde with one double bond. Patients sensitive to this substance demonstrated cross-reactivity to other essential oils of the same family such as lemongrass and even to other essential oils derived from plants of unrelated botanical origin.

In following up the work within recent years of Rothman and his co-workers and of Rostenberg and Kanof, Strauss<sup>35</sup> reported two cases in each of which the patient had an acquired sensitivity to one of a group of local anesthetics in which each compound consisted of a para-amino benzoic acid ester with a secondary or tertiary amine in the side chain. In one patient sensitivity (as manifested by patch testing) extended to the entire group of related compounds, while in the other there was no evidence (clinically or on patch testing) of any cross-sensitivity to others of the group. Strauss believes that sensitization to an entire group of structurally related compounds may occur as a result of exposure to one of the group, but this does not necessarily occur. Whether or not group sensitization has occurred must still be determined by patch testing or clinical trial in each individual case. Sulzberger et al<sup>40</sup> demonstrated that only 10 per cent of patients who developed a dermatitis from a sulfonamide ointment showed a positive patch reaction exclusively to that sulfonamide. In 90 per cent there was evidence of cross sensitization to other sulfonamides and to chemical radicals and substances related to sulfonamides.

*Rhus Dermatitis.*—The magnitude of the public health problem created by Rhus poisoning has been stressed by Turner<sup>43</sup> while calling attention to the inadequacy of preventive measures now available. The two new chemical herbicides, ammonium sulfamate and 2,4-dichlorophenoxyacetic acid (2,4-D) provide the first really promising solution to this problem.

Templeton et al<sup>42</sup> made studies on the hematologic, urinary, and temperature changes occurring during poison oak dermatitis. It was found that 80 per cent of the patients showed moderate temperature elevations, usually not above 100° F. Fifty per cent developed milk leukocytosis, and about the same percentage also showed a mild degree of eosinophilia. No urinary changes were noted.

Stratton<sup>34</sup> administered three different poison oak antigens orally or parenterally to determine their effectiveness both in prophylaxis and therapy. He found that the antigen containing lobinol, the vesicant fraction, was an efficient oral prophylactic but was less effective parenterally. The antigen containing all the fractions except the vesicant proved to be the best parenteral agent from the standpoint of prophylaxis and treatment. However, while these extracts are of value in prevention, it is now generally realized that their use in treating the acute phase of toxicodendron dermatitis is inadvisable.<sup>27</sup>

Klasson<sup>16</sup> has used ascorbic acid in the treatment of poison oak dermatitis with success. The rationale behind this form of therapy is this: It is assumed that lobinol decomposes the protein molecules of the cutaneous tissues to alkyl amines, of which histamine is one. Histamine at first produces an increased arterial pressure by direct action on the arterial wall, but ultimately increased capillary permeability results. Ascorbic acid is known to maintain vascular tone, and Klasson assumed it might counteract the toxic action of histamine. In actual practice it was found that ascorbic acid given intramuscularly in a maximum daily dose of 600 mg. definitely reduced the period of treatment. The drug may also be used orally in prophylaxis.

Robinson<sup>29</sup> found that the use of refrigerants, especially ethyl chloride, in Rhus dermatitis relieved pruritus early and considerably shortened the duration of the disease.

Witherspoon<sup>45</sup> has recommended a sodium perborate cream as a simple, efficient, and acceptable remedy for Rhus dermatitis. Nascent oxygen is released gradually and is assumed to detoxify the resins remaining on the skin.

Another warning against the use of solutions of iron salts in poison ivy dermatitis has been sounded by Strauss.<sup>36</sup> It has been known for some time that

solutions of ferrous sulfate or ferric chloride may leave residual pigmentation at the site of the dermatitis. In Strauss' patient such pigmentation slowly disappeared over a six-year period.

*Miscellaneous.*—Carpenter<sup>4</sup> has reported four cases of contact dermatitis which were followed within two to ten days by an erythema multiforme-like eruption. The author believed these sequelae were produced by the absorbed bacteria, viruses or their products from the superficially infected areas of the dermatitis venenata. In a study on pyrethrum dermatitis, Lord and Johnson<sup>19</sup> found that the dermatitis-producing factor is a distinct component of the pyrethrum flower and may be separated from the pyrethrin content. Ellis<sup>10</sup> has demonstrated that the thiosalicylic acid radical is the usual sensitizing factor in Merthiolate sensitivity. Pirila<sup>25</sup> reported six cases of sweat band dermatitis due to Thiocol (or Thioprene). Nine patients who were sensitive to an oxycholesterol-petrolatum ointment base (Aquaphor) were reported by Ellis.<sup>11</sup>

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## INDUSTRIAL DERMATITIS

The essential principles in the diagnosis, treatment, and prevention of industrial dermatitis have been reviewed by Downing,<sup>2</sup> Tolmach,<sup>10</sup> and Macanlay.<sup>6</sup> Downing<sup>2</sup> pointed out that the largest group with occupational dermatoses consists of housewives whose dermatoses are a result of exposure to soap, soap powders, squeezing oranges, handling raw fruit and vegetables, et cetera. In regard to the industrial commissioners, Downing expressed appreciation of their humane attitude: "These officials are admittedly slightly partial to the employe, and perhaps justly so. To the insurer and its representatives, either lawyers or physicians, it is just another case, the loss of which will not in any way change their routine. To the injured worker it is a tragic, all-absorbing controversy, the solution of which may determine his future and that of his family."

Tolmach<sup>10</sup> believes that the incidence of sensitization dermatitis in industry as a whole is actually less than the generally estimated 20 per cent. Furthermore, he is of the opinion that the atopic individual is not more easily sensitized in industry than so-called "normal" people. Downing, in an editorial comment,<sup>3</sup> disagreed. In his experience he found that atopic individuals should not work where they will contact sensitizing chemicals, especially where there is exposure to irritating dust, fumes, or soap mixtures. The reviewers are of the same opinion.

A number of reports on dermatitis in diverse and specialized industries have been published within the scope of this review. Samitz<sup>13</sup> found that a negligible number of dermatological cases occur in the poultry industry. There are two reasons for this: (1) The process of slaughtering and cleaning the fowl does not require the use of any chemical agent, and (2) protective clothing prevents dermatitides due to physical agents, such as friction or cold. Samitz and Gibson<sup>14</sup> found that longshoremen and harbor workers likewise have a low incidence of occupational skin disease. Among 10,700 case histories of illnesses and accidents reviewed, only 385 (3.5 per cent) had skin diseases. Parker<sup>15</sup> has mentioned some of the difficulties in the diagnosis and management of dermatitis in the shoe industry. Piriilä<sup>11</sup> completed an extensive study on occupational diseases of the skin among paint factory workers, painters, polishers, and varnishers in Finland. A total of 1,142 paint factory workers, white lead workers, and painters was studied. Of these, 119 had had an occupational dermatosis or developed an occupational dermatosis during the course of the study. The paint factory workers were divided into three groups: (1) paint workers, of whom 20 per cent developed a dermatosis, (2) washers and clearwomen, who showed a 67 per cent incidence of occupational dermatoses, and (3) outdoor workers and office employes, with only 1 per cent occupational dermatoses. Not a single white lead plant worker showed any evidence of an occupational dermatosis. Ten per cent of the painters had or had had an occupational dermatosis. Toxic dermatitis and allergic eczema were the most common manifestations of the dermatoses. In 96 per cent of the cases, the dermatosis had begun on the hands and arms; in the remaining 4 per cent, the face was first involved. There were eruptions on the trunk in only 10 per cent of the cases. Finnish sulfate and kiln turpentine were the main causes of the dermatoses. Thirty-one per cent of the total were considered allergic (sensitization) reactions; 69 per cent were considered toxic (primary irritant) reactions. Hypersensitivity could be demonstrated in only 28 per cent of the cases. The greater incidence of allergic reactions was undoubtedly due to the fact that turpentine, a strong sensitizer, was used in great abundance in the occupations presented. Disability was caused in over 50 per cent of the cases. The allergic cases were

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the most severe, were generally of longer duration, caused disability more frequently and for a longer time and compelled the workers to change occupation oftener than toxic dermatitis. Of persons engaged in the same work, a greater number of women were found to have had occupational dermatoses than of the men. Thus, in the paint factories, 30 per cent of the women but only 15 per cent of the men had acquired dermatoses.

Kilpinen<sup>5</sup> conducted a mass survey to determine the incidence of occupational eczema among bakers in Helsingfors. Only eight cases of occupational eczema were found in 653 bakers examined.

An exhaustive study on the correlation of the boiling ranges of some petroleum solvents with irritant action on the skin was completed by Klauder and Brill.<sup>6</sup> It is known that petroleum is composed of an intimate mixture of thousands of hydrocarbon compounds with paraffins ( $C_nH_{2n+2}$ ) and cycloparaffins or naphthenes ( $C_nH_{2n}$ ) predominating. Olefins, acetylenes, aromatics and other cyclic hydrocarbons are present in lesser amounts. The primary separation of petrolatum into its commercial products is accomplished by means of distillation. As a general rule, the more volatile fractions (boiling ranges below  $450^\circ F.$ ) are all primary cutaneous irritants and exert a defatting action on the skin. A solvent with a boiling range of kerosene or lower will uniformly give positive reactions on patch testing. The more viscous fractions (boiling ranges above  $600^\circ F.$ ) exert no irritant action. To reduce the hazard of dermatitis from petroleum solvents, these investigators suggest the use of a solvent for a particular job with as high a boiling range as is consistent with the purpose for which it is to be used. In jobs where kerosene is used, that of paraffinic origin should be preferred to one of naphthenic origin because the latter is more irritating. Klauder and Brill found that the cutaneous reaction to petroleum oils with boiling ranges intermediate between kerosene and the viscous lubricants varied considerably in normal persons from no reaction to varying degrees of positive reactions. The skin of negroes showed a high degree of tolerance. There was a lessened degree of tolerance of the skin of workers with dermatitis caused by solvents and of patients with dermatitis not caused by solvents. These co-workers devised a test to determine the individual tolerance to petroleum oils and solvents. Ten distillation fractions with different boiling ranges extending from that of kerosene to that of light spindle oil are used. This report should be read in its entirety by those physicians concerned with the petroleum industry or its by-products.

The chlorinated hydrocarbon solvents are high on the list of efficient degreasers. One of these, Permachlor (or trichlorethylene) is commonly used to degrease automobile motor parts. Contact with the skin produces a dry, cracking dermatitis. Safety procedures for those using this solvent have been outlined by Krieger.<sup>7</sup> Casite (a naphtha derivative) is similarly used to remove sludge from motors. It may also produce a dermatitis following skin contact.<sup>12</sup>

McKinley<sup>8</sup> had reviewed the dermatological hazards of the plastic industry. The term plastics is applied to synthetic resins. These range from solid molded materials, such as telephone receivers, to flexible sheeting, such as raincoats, shower curtains, et cetera. As a rule, the finished plastic is inert, but the chemicals used in making it may be harmful, e.g., formaldehyde. Materials known as plasticizers are added to plastics to reduce the brittleness of the plastic. These are natural gums, glycol derivatives, et cetera, and may produce a dermatitis. Stabilizers and antioxidants prolong the life of plastics by protecting them against the effects of light and heat. They include organic and metallic radicles, some of which are primary irritants. Hardeners aid in setting some resins. Hexamethylenetetramine (Hexa) is most frequently used and is a well-known sensitizer. The control of these hazards devolves upon proper ventilation, good housekeeping, showers for the employees, and frequent changes of work clothing.

Erwin<sup>4</sup> reported on skin irritations from fibreglas plastics. In most plastics the resins are of primary importance, and the filler is of secondary importance. However, in fibreglas plastic, the glass filler is the primary element. The small particles of glass are mechanical irritants and in some instances appear to be actual sensitizers. With continued employment, most workers become "hardened." However, some require transfer to new jobs. Proper clothing, protective sleeves, adequate washing, moistening of the material before it is machined or cut, and protective creams are among the necessary preventive measures. Samitz<sup>14</sup> reported three cases of fibreglas dermatitis occurring in workers repairing the insulation on refrigerators. Schwartz,<sup>15</sup> while investigating an outbreak of dermatitis from women's suits and children's coats, found that fibreglas was used as a lining for this apparel. Similar dermatitis had appeared among the girls working on the linings in the factory. Manufacturers have been advised against the use of this material in clothing.

The occupational pigmentary changes which may occur in the skin have been

reviewed by Schwartz.<sup>17</sup> These may consist of an excess of melanin or melanois, deposits of metallic substances in the skin (tattooing), and dyeing of the skin either from external application of the dye or deposition of the dye in the skin after ingestion. The occupational causes of excessive formation of pigment in the skin are (1) excessive exposure to sunlight or actinic rays, (2) exposure to coal tar, (3) exposure to crude petroleum and residuals of petroleum distillation and "cracking," and (4) exposure to asphalt. Photosensitization may develop from the last three substances named and also from exposure or ingestion of certain plants. As a result of photosensitization, protective pigmentation develops. Monobenzyl ether of hydroquinone, used as an antioxidant in rubber gloves, is the only substance known which produces an occupational depigmentation of the skin without causing a dermatitis. Apparently this compound is dissolved out of the gloves by the perspiration and absorbed into the skin where it prevents the combination of oxidase with the pigment precursor. The fact that repigmentation takes place after exposure is stopped indicates that the chromoblasts are not destroyed.

Many types of seeds are treated with organic mercury compounds to kill fungi and prevent seed rotting. Ethyl mercury phosphate or chloride, or hydroxymercuric compounds are most frequently used. Schulte<sup>15</sup> has indicated that in the actual operation of mixing this material with the seeds very few cases of dermatitis are encountered.

The importance of recognizing ragweed dermatitis when it occurs in industry is stressed by Slater et al.<sup>18</sup> If contact with ragweed is not incident to the occupation, this type of dermatitis is not compensable. The authors reported two such cases in industrial workers where their jobs, although suspected, were actually not the cause of their dermatitis.

Campbell and Schwartz<sup>1</sup> have recorded two unusual outbreaks of occupational dermatitis. Two situations were described where irritant fumes, carried in the natural flow of air from cool to warmer atmospheres, produced dermatitis in workers engaged in innocuous tasks at distant parts of large workrooms.

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#### MICROMIC ECZEMAS (BACTERIAL, MYCOTIC)

Dermatitis of the external auditory canal frequently is a troublesome disorder. Etiologically, this is not an entity. Many different factors or combination of factors may be responsible. The role of fungi has been overplayed. Pathogenic fungi may be found, but rarely. Where molds are present, they are frequently secondary invaders. Infection and infectious bacterial eczemas are rather frequent, although they may also be superimposed on other forms of eczema, especially seborrheic dermatitis and localized atopic dermatitis of the ears. *Pseudomonas aeruginosa* (bacillus pyocyaneus) was cultured by Callaway<sup>1</sup> in a case of an acute eczematoid dermatitis of the canal and pinna of the ear of a man fifty-one years of age. Routine antiseptic measures, including local and parenteral use of penicillin, failed. An aqueous solution of streptomycin containing 2,500 units per c.c. produced a rapid cure.

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According to Eva Schwarz,<sup>9</sup> skin diphtheria often presents the picture of eczema-toid or intertriginous lesions; usually it is located in the folds behind the ears, spreading from there to adjacent parts of the neck and the hairy scalp. In all twenty-four patients seen by her, the area of the ear and the scalp were affected; in nine of them there were also eruptions on the trunk and limbs. The lesions are chronic and resist the usual treatment of eczema. Mostly children, but also adults, are affected. Usually the course of the affection is benign and the general condition of the patient remains undisturbed. However, this is not always so, especially in the deeper types; even in the superficial type, there have been some cases with fatal outcome.

The treatment consisted of intensive local treatment with disinfectants such as wet applications with rivanol 1:1000, pantosept 1:1000, or Eau d'Alibour. After the regression of the acute symptoms, bandages were applied with 1 per cent rivanol vaseline, or a combination of 1 per cent rivanol and 3 per cent salicylic acid in vaseline. Later Arning's tincture (Tumenol-Ammon. 8.0, Anthrarobin 2.0, Tinct. benzoes 30.0, Ether 20.0) and Lassar's paste were used. In most cases, clinical improvement and negative smears followed this simple treatment in one or two weeks. In some instances there were recurrences and the illness lasted several months. Patients with diphtheria of the skin should be isolated because they may become the source of infection in others.

Desaux and his co-workers<sup>3</sup> report about twenty cases of different dermatoses where they have found proteus vulgaris. They found the proteus bacillus especially in eczema around the anus, with and without secondary allergic eczematization; furthermore in intertrigo. They believe that proteus also plays a role in the etiology of certain cases of vulvovaginitis and balanitis. They also have found proteus bacillus in cases of paronychia, varicose ulcer and other conditions.

Furthermore, they observed a patient with an erythematous dermatitis of the neck where they could demonstrate the presence of proteus in the stools besides enterococci, E. coli and staphylococcus. As far as treatment is concerned, proteus vulgaris in superficial dermatoses seems rather easily destroyed by the common antiseptics. When the dermatitis involves the deeper layers of the skin, surface disinfection is not sufficient; the authors recommend x-ray treatments. The allergic dermatoses due to proteus are helped by intradermal injections of an autogenous vaccine, which must be used prudently. One must be guided by the local, focal and general reactions, which are by no means rare.

Frequently they have observed positive intradermal reactions when injecting a suspension containing from 25 to 50 million germs. These were characterized both by immediate urticarial responses as well as delayed reactions after twenty-four and forty-eight hours which were sometimes painful. Although the proteus was frequently associated with other germs, especially staphylococci and Escherichia coli, the authors accord the proteus an etiologic role, because it is found only at the site of the dermatosis and possesses antigenic capacity.

Another case of eczema attributed to infection with the proteus bacillus is reported by Fejer.<sup>5</sup> The patient suffered from a generalized eczema of ten years' duration. There was an eosinophilia of 26 per cent, toxic changes in the bone marrow, a pathologic electrocardiogram and albuminuria. There existed a congenital phimosis. From the preputial sac came a purulent discharge, containing bacillus proteus. Autovaccine gave a positive cutaneous reaction. After circumcision the eczema and the general toxic condition cleared up within two weeks. Fejer considers this case an example when a microbial focus of the skin is the cause of the dermal and internal trouble. The role of focal infection in the etiology of allergic diseases is a matter of controversy at present. Epstein<sup>1</sup> feels that focal infection plays a much greater part than is generally realized. He reports two cases of a persistent localized bullous eruption which resisted anti-infectious external and internal treatment, but cleared up rapidly and permanently after the removal of infected teeth.

An interesting study regarding the relationship of intradermal reactions of the delayed type to the absorptive behavior of the skin, is presented by Seeberg.<sup>10</sup> His investigations were prompted by several observations. It is known that the tuberculin reaction may vary in strength temporarily; it is also known that the response to tuberculin can be more or less attenuated for longer or shorter periods. A transient decrease in the activity may be seen, for instance, after exposure to sunlight. Examining subjects with erythroderma, Seeberg found the disappearance time of a wheal to be very short; also the disappearance time of a tuberculin wheal was extremely short; the tuberculin failed to produce any reaction whatsoever. Seeberg presumed that this tuberculin anergy was due to changes in the absorptive capacity of the skin, leading to a rapid absorption. Seeberg used intradermal tests of the delayed type for his studies, among them tuberculin test, trichophyton test,



streptococci suspensions. Both absorption and reaction studies were carried out in different states of the skin, and compared with each other; for instance, normal skin, skin exposed, to sunlight, to mercury arc light, skin frozen with carbon dioxide, urticarial skin, edematous skin and skin changed by eczema and erythroderma. These studies showed that the absorption in normal skin is slower than that in skin exposed to the mercury arc light; slower in less-pronounced edematous skin than in more edematous skin; and slower in less-severe eczematous skin than in the more-severe eczematous stage. Experiments with tuberculin-type reactions clearly showed the significance of the absorption time. With rapid absorption there was no reaction or only a slight one. With prolonged absorption there were reactions of varying intensity. This applied both to allergic reactions, such as the tuberculin test, and toxic reactions, such as the Schick test. There were however some "paradoxical" reactions. Some of the absorption studies were carried out with radioactive phosphorus, P. 32.

#### SEBORRHEIC DERMATITIS

There is no agreement as yet among the dermatologists as to what and what not belongs to seborrheic dermatitis. What now is commonly called seborrheic dermatitis consists of a group of eczematoid eruptions. According to Darier,<sup>2</sup> they present the following four characteristics: (1) the lesions are usually dry, (2) they are sharply outlined, round, or polycyclic, (3) they persist long without a change of the clinical picture, and (4) their cure is easily accomplished by certain topical medications.

Jadassohn<sup>6</sup> stresses the following points as a distinction of seborrheic dermatitis from other eczematoid eruptions: The lesions of this dermatosis are very superficial, hardly elevated. The color most frequently varies from a pale red to a yellowish red. The scales are often of a fatty consistency; there is an outspoken tendency to peripheral growth, and often to central healing. In its pure form, seborrheic dermatitis does not present vesicles or oozing.

This typical picture of seborrheic dermatitis is seen not infrequently on the chest and back of the adults and in children. This form is recognized by everybody as belonging to seborrheic dermatitis. The etiology is unknown, but a microbial causation is assumed by many students. However, a special disposition for this disease is an important factor in its causation—a disposition which seems to be hereditary.

References to seborrheic dermatitis in the literature by no means always refer to this typical uncomplicated picture. Combinations and transitions to other forms of eczema are quite frequently found. Intertriginous dermatitis may be combined with this condition. As a whole, American literature tries to use the term seborrheic dermatitis in the more restricted sense. In the European literature, especially the British school, the term seborrheic eczema covers a wider field.

According to Lane and Crawford,<sup>7</sup> there is in seborrheic dermatitis an alteration of the function of the sebaceous glands in some individuals that leads to a so-called "seborrheic diathesis." There is hyperactivity of the sebaceous apparatus, which is sensitive to many stimuli and easily touched off into an inflammatory eruption that may appear in widespread and distressing fashion. The constitutional background obviously cannot be changed. It may be first manifested at adolescence, but endocrine therapy is fruitless. Infectious factors have not proved important, but secondary infection may be quite a problem. An environmental influence may affect some cases. Dietary approach gives inconstant results; some patients do better with a low fat intake, and others may benefit more from a restriction of carbohydrates. Large amounts of the B complex seem to help an occasional case, as do also injections of crude liver extract. No systemic approach seems to be of outstanding value.

Midana<sup>8</sup> reports the "coprologic" picture of seborrheic dermatitis of babies and children between the ages of eight months and six years (thirty patients). From the stools he studied the enzymatic activity of lipase, trypsin, amylase, and erepsin without finding any noteworthy changes compared with normals. A slight diminution of the activity of trypsin and increase of erepsin is explained by him by the increased speed of the intestinal passage so often found in tiny patients with seborrheic dermatitis. Inasmuch as he did not find an organic basis for the gastrointestinal disturbances, the author believes that they are an expression of a functional alteration, in the sense of a vagotonic reaction. The psychologic aspects of seborrheic dermatitis were studied by Wittkower<sup>11</sup> on 100 unselected cases of British military personnel. The patients revealed themselves as somewhat unsociable, shy and afraid of persons in authority. Lack of self-confidence with feelings of inferiority and insecurity caused them much anxiety at their jobs. They suffer from worries and unreasonable fears. Thirty to 40 per cent had nervous habits, such as nail



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biting or stammering; sixteen suffered from gross psychological disorders. In seventy-six of the 100 patients the onset of their skin trouble was preceded by some rather severe psychologic trauma that affected either the patient's social status or self-esteem. Wittkower stresses the point that the personality type described is very common and not specific for seborrheic dermatitis. Furthermore, only two-thirds of the patients studied conformed to it. However a comparative analysis of some striking characteristics of this personality type revealed that they were found much more frequently among patients with seborrheic dermatitis than in a control group.

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### MISCELLANEOUS ECZEMAS

Nummular eczema is discussed by Van Studdiford, McLean and Alvarado.<sup>11</sup> The term was coined by the French dermatologist, Devergie, to describe round patches of dermatitis which develop mainly on the extremities, especially the upper one. It is accompanied by redness, vesiculation, itching and a serous secretion. This is a rather common dermatologic condition. Van Studdiford and his co-workers<sup>11</sup> believe that the following are associated with the development of nummular eczema: (1) a hyperactive personality with nervous instability, (2) occurrence during the phase of diminishing gonadal activity, (3) a precipitating emotional problem, (4) a preceding minor skin disturbance which fixes the attention of the personality on the skin. These authors recommend particularly the use of pyridoxine hydrochloride. Allison<sup>4</sup> claims that these patients will improve with injections of liver extract and vitamin B complex; the reviewer<sup>5</sup> has the same impression, although it is difficult to establish definitely the value of such therapy in clinical trials. One might mention, however, the fact that Sullivan<sup>10</sup> demonstrated the role of the vitamin B complex, other than thiamine, in regard to cutaneous injuries in rats. The extent of such injuries is increased and healing is delayed where such deficiency existed.

Engman<sup>4</sup> is not prepared to accept a nervous etiology. He believes the etiology of nummular eczema is entirely unknown. The role of focal infection in this condition is considered only secondary by Van Studdiford and co-workers, but more important by other authors.

Carpenter, Nuckolls and Dyke<sup>2</sup> studied nineteen cases of nummular eczema among Navy personnel in regard to focal infection. Prostatitis was found in nine, dental infection in three, and upper respiratory foci in seven. Intramuscular injections of penicillin with gradually increasing doses from 2,000 to 15,000 units produced immediate improvement of the skin lesions, and also of the prostatitis. Two patients experienced Herxheimer-like local flare-ups.

Another stubborn eczematoid eruption of unknown etiology is the so-called exudative chronic discoid and lichenoid dermatitis or Sulzberger-Garbe disease. This is a rather rare entity. Kocsard<sup>6</sup> reports three cases; the neuropathic element was evident; two patients were cured with injections of large doses of sodium arsenate. Exfoliative dermatitis, its classification, diagnosis and treatment, is discussed by Kierland.<sup>7</sup> It should be considered a symptom complex. Exfoliative dermatitis may represent a reflection on the skin of serious systemic disease, may be an extension of a pre-existing skin disease such as psoriasis or seborrheic dermatitis, or may arise from purely local conditions, such as contact dermatitis or drug eruption. The most common complication is secondary infection of the skin. Pneumonia and hypoproteinemia are frequently encountered. Treatment is symptomatic while

a search is made for the etiologic factor. A nutritious, high protein diet should be provided; vitamins and blood transfusions are given where indicated. BAL should be given to all patients whose dermatitis is due to arsenic. Langley and Morgan<sup>9</sup> found chloroarsium (watersoluble chlorophyll in a hydrophilic ointment base) very effective in two cases of exfoliative dermatitis.

Eichenlaub and Osbourn<sup>3</sup> studied the role of the liver in congestive eczema. The commonest form is varicose eczema. Patchy eczema, usually of the legs, sometimes of the arms and trunk, was also classified in this group. (This condition probably corresponds to nummular eczema.) A series of eight such cases with disturbed hepatic function is reported by these authors. Füsthly and Pastinszky<sup>5</sup> studied the Weltmann reaction in various dermatoses, including eczemas, and consider it an exact control for disturbances of the liver.

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#### PRURITUS ANI ET VULVAE

Pruritus of the anus and vulva is a symptom. Perhaps no other eczema, except eczema of the hands, is due more to multiple causation and a variety of factors, than this condition. To the dermatologist, pruritus ani includes only those cases where there is itching without noticeable pathologic changes of the skin. In the general literature, however, the term includes all the itching eczematoid conditions of the anal region. No wonder that there is such a divergence of opinion regarding the etiology and therapy of this condition, because actually we are dealing with different entities. Atopic dermatitis, contact dermatitis, fungus infections and bacterial eczemas and their combinations, together with additional factors may be responsible. Swinton<sup>5</sup> discusses the factors that may give rise to anal itching or may cause an anal pruritus to become a definite and intractable pathologic entity and presents the methods of treatment that have proved most satisfactory in his hands.

Nearly all cases of pruritus ani are precipitated by some local mechanical factor. Anal pruritus is often initiated by a precipitating factor such as diarrhea or constipation, following which, scratching may cause local congestion, irritation, trauma and infection. This in turn causes more itching and establishes a scratch-itch cycle. The importance of avoiding irritation cannot be overemphasized. However, a wide range of factors may be responsible for the development of pruritus ani. Among the physiologic factors, Swinton mentions the irritation from soap and the sulfite in certain toilet tissues. Excessive intake of carbohydrates and fruit juices predisposed to an increased alkalinity of the affected parts. The incidence of fungous infections was not high. Pyogenic flora, with occasional streptococci, was usually found. An allergic background was encountered in a few patients. Phenolphthalein from laxatives may cause local sensitization and pruritus ani. Psychogenic factors should not be overlooked. Nervous tension, fatigue, worry, maladjustments and frustrations are frequently observed. Sexual problems may enter into many of these cases. Small amounts of tincture of belladonna with luminal is a helpful sedative. Normal bowel functions should be established. Intake of carbohydrates, roughage and alcohol should probably be reduced. Roentgen therapy is rarely used at the present time. The presence of specific dermatologic skin conditions should not be overlooked.

In certain stubborn cases search for food allergies may be necessary. Too much attention has been given to local therapy. Adequate local hygiene is important. The anal region should be cleansed routinely with cotton moistened in warm water. Toilet paper and soap are forbidden. Sitz baths in potassium permanganate

solution for fifteen to twenty minutes are used almost routinely, followed in mild cases by the application of calamine lotion with 1 per cent phenol. In severe cases continuous wet dressings and hospitalization may be necessary. In general, bland solutions are used and ointments avoided. For lubrication, castor oil or olive oil may be used sparingly. Ammoniated mercury ointment or 2 per cent silver nitrate solution may help when fissures develop. Coal tar preparations are indicated at times. Surgery has been used less and less. It is indicated for the removal of sources of infection and correction of local disease, such as infected crypts, contracted anal canal, large skin tags, anal fissures and fistulas. Alcohol injections gave temporary relief, and permanent relief in a high percentage treated with the Buie technique. However, the resulting sloughing and excessive scarring was not desirable. Alcohol injections and other radical procedures should be reserved for the severe cases. There will be a high incidence of recurrence following surgery if adequate attention is not given to the various etiologic factors.

Aldrich<sup>1</sup> believes that a fungus infection is the most common, if not the only direct cause of anal and perianal itching. However, it is considered advisable to bear in mind the predisposing and the indirect causes as well as any aggravating factors before directing attention to the local treatment. Aldrich used a 2 per cent emulsion of undecylenic acid in the treatment of fifty-four cases of pruritus ani and pruritus vulvae or both. The emulsion was applied both in the morning and at night. Fifty cases were greatly improved or cured.

Local treatment of pruritus ani with aluminum hydroxide gel is recommended by Friedman et al.<sup>3</sup> The management of pruritus ani in the armed forces is described by Marks.<sup>4</sup> Clarke<sup>2</sup> presents a case of pruritus vulvae, due to a rubber condom. From his experiments it became apparent that the irritation was due to the presence of alkali from the potassium oleate. The patient gave positive patch test reactions to caustic soda in a concentration as low as 0.05 per cent. Inasmuch as the sensitivity in this case was about sixty times that of the normal skin, the action of alkali on this woman's skin appears to be that of allergic sensitization rather than simple chemical damage.

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#### URTICARIA

The etiologic approach to chronic urticaria and angioneurotic edema is presented by Lieder and Pennock.<sup>6</sup> For an etiologic diagnosis, the first essential is a careful, painstaking, chronologic history. Attempts must be made to determine not only the specific causes, such as foods or drugs, but also the influence of emotional factors. Food factors are determined best by placing the patient on an elimination diet. During this period of elimination diet, a careful investigation should be made for possible foci of infection or infestation. Even though the most important foci of infection seem to be in the teeth, the tonsils, nasal accessory sinuses, gall bladder, prostate, cervix, appendix, and colon should be investigated. There should be stool examinations for parasites and ova. Intradermal skin tests are usually of little value. Occasionally inhalants are factors and their avoidance may aid in the treatment. The authors stress drug and bacterial allergy as being the most important etiologic factors. Food allergy is a factor in the acute urticarias more than in the chronic types. According to Kelley,<sup>4</sup> there is often a multiplicity of causes in urticaria such as food, foci of infection, bacteria and psychogenic disturbances. He considers epinephrine and ephedrine the classical therapeutic agents. Also recommended by him are calcium, synthetic vitamin K, and splenic extracts. Autogenous or stock vaccines from nasopharyngeal or stool flora occasionally may afford relief. Successful treatment of an urticaria caused by wheat bread is reported by Staufier.<sup>9</sup> The patient was treated with increasing intradermal injections of an extract made from her bread. Kaywin<sup>3</sup> points out the following six factors as possible aids in the recognition and evaluation of the role of emotional disturbances in urticaria: (1) a life situation for the period preceding the onset which is generally unhappy and anxiety-provoking; (2) sudden onset of symptoms, which has as its precipitating factor some frustrating experience; (3) a lack of an allergic history or manifestations; (4) presence of subjective and objective signs of

anxiety; (5) chronicity of symptoms; (6) a personality type characterized by shyness, easy embarrassment, blushing and immaturity with a tendency toward exhibitionism.

Menstrual urticaria has long been known to be an allergic phenomenon.<sup>10</sup> Under the title, "Erythema urticatum premenstruale," Maruri and Zorrilla<sup>6</sup> describe an erythematous-urticarial patch eruption of the hands of a young woman. The eruption always originated a few days before the onset of the menses and lasted twenty-three days. After intracutaneous injections of estradiol benzoate and progesterone, the lesions lasted six days only. Pumar<sup>8</sup> reports seven cases wherein the urticaria was completely cured by a treatment with quinine and mequin. The author emphasized the outspoken character of the urticaria and its close parallelism with malaria; in nearly every instance the skin manifestations appeared with the period of hyperthermia and receded following the crisis. In all cases the urticarial attacks disappeared, coincident with the other symptoms, with the antimalarial treatment. For this reason one may consider the urticaria to be a manifestation of the malaria.

Katzenellenbogen studied eighty cases of acarodermatitis urticaroides, a disease which is endemic in Palestine. The eruption is found in farmers, porters, drivers, milkers and stablehands and is caused by the mite *Pediuloides ventriosus*. The mites live in straw and grass, with the latter being the main source of the infestation. The forearms, neck and trunk were the parts most frequently affected, the legs rarely and only when the grass came into direct contact with the skin. The rash appeared as discrete papular lesions, lentil to bean sized, with urticarial wheals partly surmounted by tiny vesicles. The eruption lasted from six to ten days. Acarodermatitis appears in June and July and September and October. Fahlch grass which became infested with the mites was held responsible. The disappearance of the mites in the grass coincided with the disappearance of new cases of acarodermatitis urticaroides. Insects, such as mosquitoes, bedbugs and lice, may produce urticaria. Mellanby<sup>7</sup> demonstrated that the urticarial response to mosquitoes is an acquired allergic reaction. He exposed, at different periods, twenty-five volunteers who had never travelled outside Britain to the bites of *Aedes aegypti* and *Anopheles maculipennis atroparvus*. All patients showed similar reactions and no itching, but a delayed reaction occurred usually between twenty to twenty-four hours in the form of a red patch of 3 cm. in diameter, surrounding the bite, with a definite central papule. The itching lasted for several days. On the repetition of the biting by *A. aegypti*, the reaction was quite different. An urticarial reaction, highly pruriginous in nature immediately developed. This local reaction disappeared within two hours, but the delayed reaction regularly ensued. After further exposure these reactions were modified by the diminution and even disappearance of the delayed reaction. In some cases repeatedly exposed to thousands of bites by *A. aegypti*, it was observed that the immediate reaction also disappeared. The author suggests that these reactions are distinct and possibly caused by different antigens in the mosquito's saliva. It has been suggested that this increased tolerance to the bites of these pests is the result of true immunity. While a true anti-insect immunity has been demonstrated in the case of ticks, no such mechanism has as yet been proven experimentally in regard to mosquitoes. For this reason, Dubin, Reese, and Seamans<sup>1</sup> undertook experiments to see whether rabbits could be protected against mosquitoes by a course of active immunization by means of a suspension and an extract from killed, ground up, normal female mosquitoes. The authors were not able to protect rabbits against mosquitoes with this method. Moreover, the rabbits inoculated with a suspension of the mosquitoes became sensitized to mosquito bites in contrast to the normal nonsensitive rabbits. The sensitized rabbits showed large, indurated reddened papules at the site of the bites. These cutaneous reactions began in about thirty minutes, and reached their maximum size in about five hours. Attempts at desensitization of the sensitive animals were unsuccessful. Passive transfer was negative.

Urticaria from physical causes such as pressure, cold, heat and light will be dealt with in a special review on physical allergy in dermatology.

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### ANTIHISTAMINICS IN DERMATOLOGY EXPERIMENTAL STUDIES

There are contradictory reports about the ability of the antihistaminic drugs to modify or suppress experimentally produced wheals. Nexmand and Sylvest<sup>4</sup> working with lergitin (Antergan) and amidryl (Benadryl) did not observe such an effect. However, they noticed a considerable reduction of the subjective symptoms in these experimentally produced whealing reactions from histamine and others, such as urticarial skin reactions in allergic individuals, Prausnitz-Küstner test, dermatographism. In Nilzén's<sup>5</sup> experiments, simultaneous injection of the antihistaminics Antergan and Antistine with atropine, peptone, morphine and histamine produced a mild reduction of the wheal and flare caused by these substances, without the addition of the antihistaminic. Nilzén believes that these experiments support the histamine theory of Lewis. In his opinion the antihistaminics do not neutralize histamine in a chemical sense. Rather they seem to become attached to the cells and make them refractory against histamine. This can be demonstrated on the gut of the guinea pig, which remains refractory against histamine after it has been perfused with antihistaminics, even following several washings.

Borelli<sup>1</sup> studied the effect of the antihistaminic drug Dimetina (dimethyl aminoethyl benzylaniline) upon the ultraviolet reaction of the skin. In the majority of cases a rise of the threshold erythema was noted. Also an increase of the latent period and a diminution of the degree and duration of the erythema. Only occasionally was the pigmentation less severe. However, the subjective symptoms, such as burning and itching, were missing, even if they had been present and were still existing in areas that were irradiated as a control on the preceding day. Borelli concludes from his studies that a great part of the so-called antihistaminic (anti-allergic) action of these drugs is due to their anesthetic capacity.

In Olivetti's<sup>6</sup> experience the oral administration of the antihistaminic drug Dimetina did not relieve experimentally produced pruritus, although the same drug was efficacious in relieving the spontaneous pruritus of various dermatoses. Olivetti confirmed also the old observations about the ability of antihistaminic drugs to inhibit the wheal from histamine. More diluted solutions of Dimetina were more efficient in this respect. Intradermal injections of Dimetina as well as Antistin produced a moderate local anesthesia. The anesthetic action of Benadryl was studied by Leavitt and Code.<sup>3</sup> These authors compared the analgesic effect of intracutaneous injections of Benadryl and procaine. Pain thresholds were determined by the use of a simple type of an electric algesimeter. The results were as follows: By means of electric algesimetric determinations, Benadryl in dilutions of 1:500, 1:1000, 1:5,000, 1:10,000 and 1:20,000 was found to possess anesthetic potencies similar to those of procaine in dilutions of 1:200, 1:400, 1:800, 1:1,600 and 1:3,200, respectively.

Dreisbach<sup>2</sup> suggests anesthetic action may be responsible for the relief of subjective symptoms which the antihistaminic agents afford in penicillin reactions. He demonstrated that Benadryl and Pyribenzamine were ineffective in preventing the development of the Arthus type of skin reaction to penicillin in rabbits. However, mixed with histamine, Benadryl or Pyribenzamine prevented the typical skin reactions of histamine. Therefore, this author suggests that the nature of relief obtained with the "antihistaminics" is related to the central and peripheral sensory depression of these agents. Ingestion of the antihistaminic 3015 RP, which is approximately five times as effective at Neoantergan, did not influence the tuberculin reaction in children, according to Wissmer.<sup>7</sup>

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## CLINICAL OBSERVATIONS

The antihistaminic drugs are widely used and abused. As Ratner<sup>30</sup> states, they deserve a place in our armamentarium as symptomatic remedies. In dermatologic allergy, their greatest value lies in the treatment of acute urticaria and drug eruptions and in the relief of itching in a number of cases of dermatoses associated with pruritus. To Benadryl and Pyribenzamine have been added Antistine, Decapryn, Neoantergan, Theophorin and Histadyl and Thienylene, the latter two but different trade names of the same chemical. The availability of a larger number of antihistaminic or antiallergic drugs is a definite advantage for the control of pruritus. Cases that are not helped by one of these compounds may be relieved by another. Where side effects demand discontinuation or reduction of dose, another antihistaminic may be well tolerated. Although they are only symptomatic drugs, the management of the itchy patient has been made much easier since their advent.

*Antistine.*—Antistine has the advantage that it can also be given intravenously, intramuscularly and subcutaneously. Schindler<sup>33</sup> reports favorable results in eleven cases of urticaria and fifteen cases of pruritus caused by allergic factors. Schmidt<sup>34</sup> reports excellent results with Antistine in the treatment of serum sickness, drug eruption, and urticaria. In his opinion, Antistine greatly relieves the pruritus in about one-half of dermatoses treated with this drug. He used oral and intramuscular therapy; the daily doses varied between 0.1 and 0.6 gram. Especially good results with Antistine are reported by Kallos.<sup>17</sup> All sixty-two cases of acute urticaria were improved. He used rather large doses, 100 mg. six times daily orally and/or parenterally. In Britton's<sup>5</sup> experience, Antistine was of benefit in only five of eleven cases of urticaria.

*Benadryl.*—Benadryl gave relief in about 90 per cent of acute urticaria in the experience of Lynch<sup>22</sup> and of O'Leary and Farber.<sup>25</sup> Twenty-four out of twenty-nine patients with urticaria had pronounced relief in Blumenthal and Rosenberg's<sup>4</sup> experience. Lynch found Benadryl especially effective in the treatment of urticarial hypersensitivity to drugs. Benadryl gave relief to about 60 per cent of eleven patients with insect bites. He also obtained approximately 60 per cent relief in patients with vulval pruritus. The results were encouraging, but inconclusive, in erythema multiforme, rosacea, and lupus erythematosus. There was failure in various forms of eczema and dermatitis herpetiformis. According to O'Leary and Farber, the edema present in scleroderma and acrosclerosis can be relieved temporarily with Benadryl therapy. In seven of nine patients with these conditions, movements of the fingers and hands were easier. Only two of the seven patients, however, had sustained relief. In 31 per cent of the patients in this series, toxic reactions to Benadryl were exhibited. In regard to atopic dermatitis, only eight of twenty-five patients of O'Leary and Farber were relieved of pruritus. However, in certain forms of contact dermatitis, Benadryl seems superior to other antihistaminics. Loveless<sup>21</sup> states that the itching, but usually not the lesion of poison ivy and similar eruptions of the contact type of eczematous dermatitis, yielded to Benadryl in three-fourths of the eighteen patients treated.

*Decapryn.*—Decapryn is another new histamine antagonist. In the experience of Brown, Weiss, and Maher,<sup>6</sup> generalized pruritus was relieved in one-half the patients. There was significant relief in erythema multiforme, but no relief in two patients with contact dermatitis from poison ivy. Drowsiness was the most commonly encountered side effect, and was observed in about one patient out of six. Of the patients who had previously taken other antihistaminics, most preferred Decapryn. The authors consider Decapryn a valuable addition to the antihistaminics or anti-allergic agents.

*Histadyl.*—Histadyl showed its greatest effect in acute urticaria, according to Pierce and Mothersill.<sup>28</sup> In the reviewers' experience this drug has been satisfactory in pruritus ani et vulvae and in relieving the pruritus of atopic dermatitis and of the atopic eczema of the hands. In doses of 200 mg. daily, or less, the incidence of side effects has been exceedingly low.

*Neoantergan.*—Neoantergan malate, in daily total doses from 0.3 to 0.8 gm.,

relieved the symptoms in eight cases of chronic urticaria in Hunter's<sup>17</sup> experience. Six cases of acute urticaria were treated successfully.

*Pyribenzamine*.—Kesten<sup>19</sup> treated 280 patients with dermatoses associated with marked pruritus. The average oral dose was 50 mg. after each meal and 100 mg. at bedtime. Pyribenzamine was beneficial in the treatment of approximately 68 per cent. Prompt and complete relief was obtained in patients with serum sickness and in many patients with urticaria due to penicillin. The continued use of Pyribenzamine effectively controlled most physical allergies and dermatographism. Pyribenzamine completely relieved or controlled the symptoms in 65 per cent of patients with urticaria, and depressed itching in approximately 60 per cent of patients with allergic eczema, 40 per cent with dermatitis venenata, and 75 per cent with pruritus. Pyribenzamine was discontinued in about 13 per cent of the patients because of side effects. The results of Baer, Sulzberger and Witten<sup>3</sup> are less optimistic in regard to itching dermatoses other than urticaria. They noted a strong antipruritic effect in only about 10 per cent of these cases treated with Pyribenzamine and Benadryl.

*Thephorin*.—Reynolds and Horton<sup>32</sup> report on Thephorin. One out of three cases with acute urticaria gave an excellent result. Three cases of chronic urticaria were not relieved. However, the antihistaminic effect seemed apparent from its efficiency in cold urticaria and one case of hives following intravenous histamine therapy.

*Thenylene*.—Seventy-two patients with a variety of dermatologic conditions were treated with Thenylene by Kierland.<sup>20</sup> Best results were obtained in urticaria and angioneurotic edema. Of nineteen patients with atopic dermatitis, those who had urticarial lesions gave the most satisfactory response. Four out of five patients with anal and vulval pruritus were helped. Similar results with thenylene are reported by Feinberg.<sup>14</sup>

*Vitamin D<sub>2</sub>*.—There appears some chemical relationship among most of the antihistaminics used so far. Apparently other chemicals also have some antihistaminic or antiallergic property. Dainow<sup>7</sup> treated guinea pigs with subcutaneous injections of massive doses of vitamin D<sub>2</sub>. He injected 900,000 units of the Vi-De super-concentrate (Wander) twice at one week's interval. He was able to protect them from the bronchial spasm, which is produced by spraying histamine and acetylcholine in animals that were not treated with vitamin D. Dainow considered this as an indication that vitamin D<sub>2</sub> possesses antiallergic property. This explains the same author's previous observation (1939) that occupational eczemas can be favorably influenced by vitamin D<sub>2</sub> treatment, even if the patient continues working in the same environment.

## COMPARATIVE CLINICAL STUDIES ON THE ACTION OF DIFFERENT ANTIHISTAMINICS

Clinical comparisons of this kind are subject to various sources of error. A. and S. Friedlaender<sup>15</sup> have tried to overcome these difficulties in a careful comparative evaluation of Antistine and Pyribenzamine. Both drugs were at times prepared in capsule form and alternated without the knowledge of the patient. Placebo capsules were also used in eliminating as far as possible the psychologic factors involved in drug administration. Pyribenzamine was usually more beneficial in urticaria. In only one case of this type was Antistine found more helpful. Pyribenzamine appeared to be slightly more effective in relieving the distress accompanying pruritic skin conditions. In a group of seventy-two patients who received both drugs, the incidence of side effects from Antistine was 18.05 per cent, as compared to 38.8 per cent from Pyribenzamine. Of the twenty-eight patients who experienced unpleasant reactions from Pyribenzamine, eighteen were able to take an effective dose of Antistine (50 to 100 mg.) without difficulty. The remaining ten individuals experienced essentially the same reaction from either drug. On the other hand, only three out of thirteen patients noting side effects from Antistine were able to tolerate a 50 mg. dose of Pyribenzamine. Comparing the results of the same two drugs in rather small groups of patients, Watson<sup>30</sup> had better results in urticaria with Antistine than with Pyribenzamine, whereas in atopic dermatitis Pyribenzamine afforded greater relief. The latter observation agrees with the experience of the reviewers.

Kierland<sup>20</sup> noted a high degree of similarity in a clinical dermatologic comparison of Thenylene, Benadryl and Pyribenzamine. In atopic dermatitis, Benadryl made a better showing, which Kierland attributes to its greater sedative effect.

Compiling 3,600 observations from the literature and adding 200 of her own, Lowcless<sup>21</sup> states that there is little difference between the efficacy of Benadryl and Pyribenzamine.

## ANTIHISTAMINICS IN CONTACT DERMATITIS

Blumenthal and Rosenberg<sup>4</sup> obtained encouraging results in a small series of patients with contact dermatitis. Kierland<sup>20</sup> obtained good results with Thénylène in individuals who had acute dermatitis venenata. The reviewer can confirm this experience. However, the efficacy of antihistamines in contact dermatitis is denied among others by Sulzberger,<sup>35</sup> Osborne,<sup>26</sup> as well as O'Leary and Farber,<sup>25</sup> Tweedall and O'Connor.<sup>38</sup> Pyribenzamine did not alter the patch test response in five patients that gave 4+ reactions to poison ivy. Only one had some relief of subjective symptoms. Mayer<sup>23</sup> states that experimental sensitizations of the contact type dermatitis are much more resistant to treatment with Pyribenzamine, although in almost all cases the antihistaminic compound had a definite beneficial influence. However, in no animal was there complete protection. Mayer<sup>24</sup> also reports that Pyribenzamine suppresses or attenuates the initial state of skin irritations in guinea pigs, produced by primary irritants. Aaron, Peck and Abramson<sup>1</sup> were also able to suppress or reduce the intensity of patch test reactions by preceding iontophoresis with Pyribenzamine. With the same technique, these authors also inhibited dermatologic reactions due to primary irritants in guinea pigs.

It seems to the reviewers that there are several plausible explanations for these controversial findings and opinions. The different cases of contact dermatitis are not all identical from an immunologic point of view. Epidermal sensitivity is present in most cases, but not in all.<sup>9</sup> However, in addition to this epidermal sensitivity there may be also dermal sensitivity, either or both of the urticarial type<sup>38</sup> or of the tuberculin type.<sup>9</sup> The former combination is found frequently in clinical poison ivy dermatitis. These cases seem to be those that respond to Benadryl in regard to subjective symptoms. Tuberculin-type sensitivity in contact dermatitis is recognized especially in those cases that are sensitive to nickel, chromates, weeds, drugs and probably also in dermatitis from paraphenylenediamine, which Mayer used in his experiments. The efficacy of antihistaminic drugs in these cases is not as pronounced or regular as in the former, but in some instances rather gratifying. Dosage may be an additional factor. In Mayer's<sup>23</sup> experiments 0.5 mg. to 1 mg. of Pyribenzamine per kilogram body weight gave effective protection to more than 50 per cent of sensitized guinea pigs in regard to anaphylaxis; in vascular sensitization of guinea pigs to hog serum doses of 10 to 25 mg. per kilogram body weight were required to prevent or suppress completely the symptoms. In epidermal sensitivity the same large doses were required, but still only with partial success. Inadequate dosage is also claimed for failure of clinical response to Benadryl, by Reinstein and McGavack.<sup>31</sup> Another factor, explaining the discrepancy of opinion of the value of antiallergic drugs in contact dermatitis may be the differences of pharmacologic action. The relief obtained may not be due to their antihistaminic efficacy, but to their anesthetic or sedative action. That could explain the superiority of Benadryl in these cases, as this drug appears to have the most pronounced sedative effect.

## TOPICAL USE OF ANTIHISTAMINICS

Feinberg and Bernstein<sup>13</sup> treated patients with itching dermatoses with a 2 per cent Pyribenzamine ointment. They obtained relief in the majority of cases, particularly atopic dermatitis and pruritus ani; Sulzberger, Baer and Levin<sup>36</sup> could not fully confirm these findings. They had good results in lichen simplex chronicus circumscriptus (circumscribed neurodermatitis, localized atopic dermatitis). Of sixteen cases, eight showed definite improvement and four additional cases transitory improvement in pruritus and clinical course. However, of forty patients with atopic dermatitis (disseminated neurodermatitis) only two showed transitory improvement in pruritus, twenty-five showed no change and thirteen were made worse. Of a total of ninety cases, two developed an allergy of the eczematous contact type to Pyribenzamine and two presented systemic symptoms, such as vertigo, palpitation or "jittery" sensations.

Aaron, Peck and Abramson<sup>1</sup> treated a total of twenty patients with iontophoresis of Pyribenzamine. There were seventeen cases of chronic lichenified eruptions and one case each of Sulzberger and Garbe's syndrome (see above), generalized exfoliative dermatitis and atopic dermatitis. In every case there was some relief from pruritus and clinical improvement. There was a complete remission in the majority of cases. Ten per cent and 5 per cent solutions of Pyribenzamine were



used, which were introduced into the skin through the positive electrode. Daily (localized atopic dermatitis). However, this cream has been quite helpful in a few cases where oral Pyribenzamine had failed.

Perry<sup>27</sup> used a 2 per cent cream of Benadryl in a water-soluble base. Local application of this cream did not influence the erythema and wheal produced by an intradermal injection of histamine. Of twenty patients with various pruritic dermatoses, six had moderate and two had excellent relief from the ointment base alone.

Experience with a 2 per cent Histadyl cream<sup>10</sup> has also shown that the best indication for antihistaminic creams is the circumscribed lichen simplex chronicus (localized atopic dermatitis). However, this cream has been quite helpful in a few cases of generalized atopic dermatitis, as well as infantile eczema of the atopic type and in pruritus ani et vulvae, although it has failed in quite a number of similar cases. The differences of opinion and results regarding antihistaminic ointments may be attributed not only to the different antihistaminics and ointment bases, but also to the selection of cases. Water-soluble creams should be used only in chronic eczemas, not during the acute phase.

The side reactions of the antihistaminics are reviewed in the chapter on drug eruptions.

General reviews about the antihistaminics are presented by Feinberg,<sup>12</sup> Hartman,<sup>16</sup> Rajka.<sup>29</sup>

### OTHER ANTIPRURITIC DRUGS

A number of vasodilator drugs are effective antipruritic agents. In an attempt to find a vasodilator free of undesirable side effects, Wirth<sup>40</sup> tried papaverine hydrochloride, an opium derivative. It is a mild sedative and may cause sleepiness when given in large doses. Papaverine hydrochloride was taken by a group of twenty-nine patients uncomfortable because of itching due to various causes, including dermatitis venenata, postscabetic sulfur dermatitis, insect bites, et cetera. The drug exerted an antipruritic effect in all twenty-nine cases—complete in twenty-six and moderate in three. Intravenous injection (1 grain), given slowly, gave consistent prompt relief lasting one to six hours. Oral administration (grains 1½) gave relief in about thirty minutes, but papaverine hydrochloride may be ineffective by mouth.

Ervin Epstein<sup>8</sup> treated seventeen patients suffering from various itching dermatoses with intramuscular injections of aminophylline. In all instances the itching had resisted conventional antipruritic measures. The dosage was 0.5 gm. of aminophylline administered intragluteally in 2 c.c. of fluid. In seven patients the relief of itching was dramatic; the itching subsided within thirty to forty-five minutes and did not recur until twelve to thirty-six hours later. However, the over-all results were not so successful as some of the other patients experienced temporary relief only. A high frequency of reactions was noted. These included numbness and stiffness of leg, pain at site of injection, nausea and symptoms of shock. It seems, therefore, that the toxicity and the short duration of its effect would prevent the general use of intramuscular injections of aminophyllin as an antipruritic agent.

Hydrillin (Benadryl and aminophylline) seemed to relieve the pruritus in several cases of disseminated atopic dermatitis as well as the generalized id-like eruptions associated with some cases of contact dermatitis,<sup>11</sup> especially in older patients. One tablet of 100 mg. Hydrillin was given four times a day.

In general, however, the older systemic antipruritics are taking a back seat behind the antihistaminics. Ergotamine tartrate relieves pruritus,<sup>2</sup> but gangrene may result. Lichtman in 1931 gave 1 mg. three times a day and stopped as soon as there was relief. He got good results. But later workers had some unfortunate experiences, including death after four days in one case, and amputation of both legs for gangrene in another. Though these ill effects are rare, the risks are too serious to warrant the use of the drug, when the antihistamine drugs are available instead.

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## DRUG ERUPTIONS

Several recent articles have discussed the general concepts of drug allergy.<sup>28,64,113</sup> Dragstedt<sup>28</sup> divides drug idiosyncrasies into the allergic and nonallergic and offers the following provisional criteria to distinguish between the two types: (1) An allergic basis seems to be indicated when the pattern of the toxic reaction is consistent with that of the allergic disorders produced by antigenic agents. This means that reactions characterized by urticaria, dermatitis, angioneurotic edema, and asthma are probably allergic in character; that reactions characterized by jaundice, acute yellow atrophy of the liver and optic atrophy are probably not allergic, while granulocytopenia, anemia, thrombocytopenia, and polyneuritis may well be one or the other. (2) An allergic basis seems to be indicated when a priming or sensitizing administration of the drug appears to be a factor in the history, while a nonallergic basis seems to be indicated when either long continued administration or the use of substantial doses appears of major importance. (3) An allergic basis seems to be indicated when the untoward reactions are alleviated by epinephrine, diphenhydramine hydrochloride (Benadryl Hydrochloride N.N.R.) and similar agents, whose ameliorating effects are most reasonably interpreted on the basis of an anti-allergic effect. A nonallergic basis seems to be indicated for those reactions which are alleviated by ascorbic acid, folic acid, thiamine and other agents whose ameliorating effect is not reasonably credited to an antiallergic effect.

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### PENICILLIN

*Parenteral Penicillin Administration.*—The various reactions to parenteral injections of penicillin have been reviewed by several authors.<sup>45,52,74,75,79,98,104</sup> According to Peck,<sup>78</sup> there are two distinct reactions of sensitivity to penicillin. One is the serum sickness-like urticarial type which is an induced sensitivity, and the other is the eczematoid-trichophytid-like type which may be based on a previous sensitivity produced by a fungus infection. To this latter group belong the so-called "spontaneous" penicillin sensitive cases. Steingold<sup>98</sup> believes penicillin reactions are more common in males than in females.

Exfoliative dermatitis occurring during penicillin administration appears to be of rare occurrence. In the discussion which followed Templeton's paper on cutaneous reactions to penicillin,<sup>104</sup> Lehman reported that he had seen two cases of exfoliative dermatitis originating from this source, and Wile reported seeing six such cases. In all instances the condition was mild and not comparable to exfoliative dermatitis due to arsenicals. Farrington and Tamura<sup>86</sup> reported the case of a seventy-eight-year-old man, ill with pneumonia, whose critical condition necessitated continuing penicillin therapy in spite of a maculo-papular reaction. An exfoliative dermatitis ultimately developed. Later, when the skin was clear, the patient showed urticarial and tuberculin-type reactions on testing with various commercial brands of penicillin. Patch tests were also positive. There were no reactions from autoclaved material or penicillinase-inactivated extracts.

One of the most unusual reactions to penicillin is that reported by Call and Gilbert.<sup>15</sup> Their patient received penicillin injections eight times within a one-year period. After each episode, abscesses developed at the penicillin injection sites. Since the injections had been given at several different army hospitals, it seemed incredible that the penicillin was contaminated in each instance. In studying this patient, the authors were able to produce a sterile abscess at the site of a penicillin injection while controls, injected with the same solution, remained normal. There is no similar case reported.

Kendig and Toone<sup>56</sup> reported three cases of delayed "serum sickness" type penicillin reaction occurring in the same family within a six-week period. All three patients manifested moderate fever, malaise, arthralgia, and urticaria. Two of the cases had previously received penicillin.

Barefoot and Orlandky<sup>6</sup> have reported an interesting case. Their patient was given injections of noncrystalline sodium penicillin on two occasions at an interval of ten days. On each occasion only a few injections were given because the patient developed urticaria. In addition to this, on the second occasion there was also a flare-up of a chronic tinea cruris and a chronic dermatophytosis of the feet. At this time intradermal tests showed a definite reaction to noncrystalline sodium penicillin while crystalline penicillin produced no reaction. Thereupon, the patient was given and tolerated full therapeutic doses of crystalline penicillin G. The authors pointed out that, in some patients at least, reactions have been observed with the use of commercial penicillin which are due to the incorporated impurities rather than the penicillin *per se*. Steingold,<sup>98</sup> in reviewing four cases of penicillin urticaria, performed intradermal tests with pure and commercial penicillin. All four patients showed reactions to commercial penicillin but not to pure penicillin. This author also believed the urticaria was an allergic response to impurities in the commercial preparation. Peck and Siegal,<sup>78</sup> after sensitizing a guinea pig with amorphous penicillin, were able to demonstrate a positive Dale reaction with amorphous but not with crystalline penicillin. This adds further proof to the impression that impurities in commercial penicillin probably are responsible for some of the allergic reactions seen.

*Local Use of Penicillin.*—Papers concerning the topical use of penicillin in dermatology have been presented from several sources. MacKenna<sup>65</sup> reviewed the principal British contributions on this subject. Hellier<sup>50</sup> indicated that the number of skin conditions which respond dramatically to local penicillin is actually quite small. Hopkins and Lawrence<sup>53</sup> sought to answer the question: Does treatment of superficial lesions with penicillin sensitize some individuals sufficiently to prevent internal treatment which might later be critically needed for some general infection? These investigators found that only about one half of the patients whose sensitivity was demonstrable by patch or intradermal tests reacted when tested by intramuscular injection. Moreover, it was shown that epidermal sensitization to penicillin is frequently local and transitory, and reactions are comparatively mild. It was concluded that sensitization to penicillin by topical application severe enough to prevent or prohibit systemic treatment with penicillin occurred in less than 1

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per cent of such cases. Meara<sup>68</sup> described three cases of dermatitis which had skin sensitivity to certain penicillin preparations. In all three it was found that the penicillin was not the responsible agent.

*Other Routes of Penicillin Administration.*—There appears to be a considerable difference in the sensitizing potential of penicillin when applied to different areas of the skin and to different mucous membranes. The apparent greater susceptibility of the face and mouth to sensitivity reactions from contact with penicillin as compared to other body regions and mucosal structures has been noted by Farrington,<sup>31,32</sup> Hopkins and Lawrence,<sup>33</sup> in studying sensitization from topically applied penicillin, demonstrated that often only restricted areas of the skin showed epidermal sensitivity.

In using penicillin aerosol for respiratory infections, stomatitis, nasal irritation, and dermatitis around the nose and mouth occurs in about 5 per cent of patients.<sup>38,82</sup> Stomatitis after oral administration of penicillin has been observed in 14 per cent of patients so treated.<sup>35</sup> This is in marked contrast to the utter lack of sensitivity reactions following vaginal administration of penicillin. This route of administration was apparently first utilized by Goldberger et al.<sup>12</sup> They demonstrated that penicillin is readily absorbed through the vaginal mucosa and appears in the blood in high therapeutic levels. Absorption from the vagina was found to be somewhat slower and more prolonged than absorption after intramuscular injections. Wide individual varieties in blood levels obtained may, in part, be due to leakage from the introitus. The method has the advantages of being painless, and the patients may insert the suppositories themselves. In ten patients treated by this method no untoward local or systemic toxic effects were observed. Pierce, as quoted by Farrington,<sup>35</sup> has used vaginal suppositories containing 300,000 units of penicillin in over 500 obstetrical patients immediately after delivery without encountering a single toxic or allergic reaction. Goldman and Feldman,<sup>44</sup> studying the sensitizing properties of penicillin for the vaginal and rectal mucosa, observed no reactions when suppositories containing 100,000 units of penicillin were used by thirty patients over an average period of one week. These authors also devised a method of contact testing of the vaginal mucosa. No reactions were seen in five patients tested with penicillin. Abel et al.,<sup>1</sup> while investigating the use of penicillin vaginally, found that the degree of absorption and the resulting blood levels were unreliable and unpredictable. They advocated that this route of administration be used only for inflammatory conditions localized to the vaginal area. It is interesting to note that two of nineteen nurses being used as control subjects developed urticaria during the study of vaginal penicillin absorption.

*Demonstration of Circulating Antibodies in Penicillin Sensitization.*—Evidence in favor of the presence of circulating antibodies in at least some penicillin reactions has been presented by Holden<sup>52</sup> and Templeton et al.<sup>104</sup> These investigators performed passive transfer tests using serum from patients with penicillin reactions. They were able to demonstrate reactions at the test injection sites when challenged with a penicillin solution. Peck and Siegal<sup>78</sup> were not able to demonstrate the presence of anaphylactic antibodies when the serum of a patient with known penicillin sensitivity was injected into guinea pigs prior to performing the Dale test. However, as realized by these investigators, no general conclusions can be drawn from an isolated observation.

*Penicillin Desensitization.*—If a reaction occurs during parenteral penicillin therapy it does not necessarily preclude the possibility that penicillin may be tolerated at a later date. There is evidence to show that penicillin sensitivity may be of relatively short duration and may decline rapidly.<sup>53</sup> In some instances the sensitivity to penicillin will decrease over a period of six months to a year so that a second course may be given without reaction.<sup>84</sup> The interval may be shorter, but certainly only rarely less than six weeks.<sup>98</sup> On the other hand, each subsequent attack may tend to increase the degree of sensitivity still further with increasingly severe reactions.<sup>122</sup> As a general rule, it is advisable to test such patients with small trial doses to determine if sensitivity still exists before again starting full therapeutic doses. Positive intradermal tests are not in themselves sufficient reason to assume that sensitivity of such a degree exists as to preclude intramuscular injections of penicillin. The intradermal test may be positive and the patient still tolerate penicillin administration via the intramuscular route.<sup>53</sup> If a reaction recurs with a trial dose, desensitization may be attempted.<sup>3,79,89</sup> Peck et al.<sup>79</sup> have reported the case of a sixty-three-year-old man who had previously developed a generalized eruption following penicillin injections. One month later a forty-eight-hour intradermal test to noncrystalline penicillin was

positive. Four months later it became imperative to give him penicillin again. Intradermal tests were still positive. Thereupon, an attempt at desensitization was undertaken. Injections were given subcutaneously three times a week starting with 400 units of noncrystalline penicillin. Each subsequent dose was doubled. When the dose reached 20,000 units, a skin test with penicillin gave only a pinhead sized papule at forty-eight hours. Intramuscular injections were then started and built up to 30,000 units every three hours. At this time a cutaneous reaction appeared in the groins. Treatment was stopped for twenty-eight hours, the dosage reduced, started again, and gradually brought back to the maximum level. The eruption in the groins gradually faded. The patient was later tested with both crystalline and commercial penicillin with negative results.

*Intravenous Procaine Treatment of Penicillin Reactions.*—Intravenous procaine has been used in treating serum sickness-like penicillin reactions according to the procedure outlined by State and Wangenstein. Dressler and Dwork,<sup>30</sup> in treating a patient with such a reaction, observed dramatic subsidence of the urticarial rash, and regression of the leukocytosis, fever, and arthralgia. Cohen and Kaufman<sup>20</sup> treated four cases of serum-like reactions due to penicillin with intravenous infusions of procaine. Two of the cases showed a favorable reaction. The other two did not respond. These authors cautioned of the possible dangers involved in this procedure. This warning was given earlier by Waldbott,<sup>108</sup> who pointed out that sensitivity to cocaine and related drugs is not uncommon and allergic shock may occur during such infusions. Preliminary skin tests are unreliable. He reported a case where the patient developed severe allergic shock after receiving 0.5 gm. procaine hydrochloride intravenously for relief of an urticarial reaction from penicillin. On the other hand, Graubard et al<sup>47</sup> have administered over 2,000 intravenous procaine infusions for control of pain without serious complications. It would appear that allergic reactions from intravenous procaine are uncommon. Nonetheless, they constitute an ever-present danger. The procedure should be done in a hospital under controlled conditions, and then only after careful consideration. Pillsbury and his group,<sup>51</sup> using Benadryl and Pyribenzamine, have outlined a more conservative approach to the management of urticaria due to penicillin. Dreisbach,<sup>29</sup> in animal experiments, has shown that any effect obtained in this condition with the antihistaminics is subjective and is probably due to central depression or local anesthetic action. This investigator has expressed doubt that free histamine is liberated in the skin sensitization reaction to penicillin and horse serum.

*Cross Sensitization to Penicillin and Trichophyton.*—There appears to be a difference of opinion regarding the presence of a common antigen in trichophyton and penicillin. Cormia, Lewis and Hopper,<sup>21</sup> after a series of guinea pig experiments, presented evidence of a crossed reactivity in penicillin and trichophyton sensitization. Their results confirmed the supposition made by many workers that a common antigen is present in penicillin and in pathogenic fungi causing superficial fungus disease. They believe that the shock-like reactions developed shortly after institution of penicillin therapy are due to pre-existing sensitization by pathogenic fungi. On the other hand, Peck and Siegal<sup>78</sup> were not able to demonstrate a single positive Dale reaction to trichophyton in guinea pigs injected with amorphous penicillin. This, plus other observations, led these authors to conclude that the dermatophytes produce penicillin or a penicillin-like substance and thus sensitize the skin to this substance just as they do to trichophyton. Penicillin sensitivity, thus induced, is independent of trichophyton sensitivity. They are often associated because of their common origin. These authors proved, by a series of clinical observations and experiments, that there is no common antigen between crystalline penicillin and trichophyton. Penicillin sensitivity can exist in the absence of trichophyton sensitivity.

*Dangers in the Indiscriminate Use of Penicillin.*—Aside from the development of sensitivity, there is another good argument against the indiscriminate use of penicillin. The widespread use of the drug, particularly in inadequate dosage, is a potent factor in breeding resistant strains of organisms.<sup>32</sup> Barber<sup>5</sup> has pointed out a notable increase in the resistance of certain organisms, especially staphylococci, to penicillin year by year since the drug was first introduced. In analyzing a series of 100 patients with staphylococcal infections seen during the first half of 1947, this investigator found no less than thirty-eight with penicillin-resistant strains! According to Florey,<sup>39</sup> there is no significant cross resistance between the various antibiotics, e.g., a penicillin-resistant staphylococcus may be rather sensitive to helvolic acid or many other antibacterial substances. He hastened to add, however, that most of these other antibiotics which have been investigated are toxic to animal

tissues or have other disadvantages. It would appear that penicillin is quickly expending its usefulness. However, Voureka<sup>107</sup> has recently dispersed some of the gloom associated with this problem. From his studies it appears that when some penicillin-resistant strains grow in association with other bacteria—a condition which may happen in the body—they lose their resistance and again become penicillin susceptible. Voureka's work along these lines is continuing, and other valuable information may be forthcoming.

Experiments have shown that penicillin in high doses exerts a pharmacologic oxytocic action on isolated strips of guinea pig uterine muscle.<sup>78</sup> These experimental observations lend support to the contention of some that penicillin during pregnancy may be responsible for early miscarriages.

### STREPTOMYCIN

This antibiotic, derived from the actinomycetes, is the drug of choice in many infections due to Gram-negative bacilli and to *Mycobacterium tuberculosis*. Four general types of toxic reactions to streptomycin have been observed: (1) the so-called histamine reaction, characterized by flushing, headache, and an abrupt fall in arterial pressure, (2) various other manifestations of sensitivity, (3) a neurologic disturbance characterized by vestibular dysfunction and occasionally by deafness, (4) evidences of renal irritation manifested by cylindruria and occasionally accompanied by impairment of renal function. The histamine-like reactions reported by early investigators were probably due to impurities in the drug. However, the other types of toxic reactions have continued to appear even with the use of highly purified material. Some of these reactions may still be due to remaining impurities, but it is probable that some of the pharmacodynamic effects observed are intrinsic properties of the drug.<sup>70</sup> The various sensitivity reactions to streptomycin are chiefly of interest to us. Contact dermatitis, developing in those administering the drug, is discussed elsewhere in this review.

Eruptions developing during streptomycin therapy have been reported from several sources.<sup>2,24,37,56,83,97</sup> The type of eruption is by no means constant. For example, maculopapular, erythematous, erythema-multiforme-like, urticarial eruptions and exfoliative dermatitis have all been mentioned. Eruptions have occurred most commonly in those undergoing long courses of streptomycin therapy, such as is required in the treatment of tuberculosis. Chinn et al.<sup>37</sup> treating seventy-seven gonorrhea patients, observed no skin reactions following single injections of streptomycin in doses varying from 0.1 gm. to 0.5 gm. Where treatment has been prolonged, eruptions have occurred most often between the seventh and tenth days.<sup>24,37,83,97</sup> To Steiner and Fishburn<sup>97</sup> this occurrence recalled Milhan's "erythema of the ninth day" which supposedly is due to an activation of a pre-existent latent infection (biotropism). These authors felt that eruptions from streptomycin were not of a toxic but of an allergic nature. And such they no doubt are. The incidence of eruptions occurring during extensive streptomycin therapy has been reported as 18 per cent,<sup>97</sup> 12 per cent,<sup>37</sup> 7.5 per cent,<sup>55</sup> and "a considerable percentage of cases."<sup>24</sup>

In cases where the eruptions are mild and without systemic reaction, treatment with streptomycin may apparently be continued without any untoward sequelae. Thus, Steiner and Fishburn,<sup>97</sup> and Kane and Foley<sup>55</sup> did not consider the mild eruptions which they observed as contraindications against further necessary or desirable treatment with streptomycin. There were no ill effects. On the other hand, when a generalized exfoliative dermatitis threatens or develops, it constitutes an indication for immediate cessation of therapy. Seven such cases (0.80 per cent) were recorded in the Report of the Council on Pharmacy and Chemistry.<sup>24</sup> Unfortunately, the details of these cases were not given. In the Report of the American Trudeau Society<sup>2</sup> mere mention is made that exfoliative dermatitis is observed very rarely. Pulaski and Seeley<sup>83</sup> observed four instances of exfoliative dermatitis among 1,153 patients treated with streptomycin. Where there is any question of the dangers involved, it is probably advisable to discontinue treatment and resume it later when evidence of hypersensitivity has disappeared. This was the procedure followed by Farrington and his group<sup>37</sup> in two cases who developed a pruritic skin eruption with a rise in temperature, nausea and vomiting, and hypotension after nine days of treatment. In both, clinical evidence of sensitivity subsided in one week. Thereafter the patients were tested every week with small doses of streptomycin, and mild symptoms were reproduced while sensitivity still existed. At the end of four and eleven weeks, respectively, evidence of sensitivity could no longer be demonstrated and a full treatment schedule was resumed.

The Report of the Council on Pharmacy and Chemistry<sup>24</sup> states that Benadryl was usually effective in relieving the pruritus of streptomycin eruptions. However,

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Steiner and Fishburn found that the eruptions were apparently little influenced by treatment which in their cases consisted in the main of calcium gluconate, Benadryl and ephedrine.<sup>97</sup>

Some degree of eosinophilia (commonly of the order of 10 to 20 per cent) is observed early in the course of treatment with streptomycin whether or not a skin eruption is produced.<sup>24,37,97</sup> It is frequently intermittent and often persists until treatment is stopped. It is not of itself an indication for cessation of treatment.<sup>24</sup>

Peck and Siegal<sup>78</sup> showed that in guinea pigs injected with penicillin there was not a single Dale reaction to streptomycin. In the streptomycin-injected animals, however, two of the animals showed reactions to amorphous and crystalline penicillin. These experiments suggest that streptomycin as now available contains an antigen closely related to penicillin. It may even be penicillin itself. The authors therefore suggest caution in employing penicillin in patients who have shown reactions to streptomycin.

### TYROTHRIN

In contrast to penicillin and streptomycin, tyrothricin, an antibiotic derived from bacteria, appears to have a very low sensitizing index. In fact, these reviewers have been unable to find a single report of serious untoward reaction from topically applied tyrothricin. Sulzberger and Baer<sup>100</sup> have reported using Tyrothricin Intra-derm in hundreds of cases without encountering an instance of true eczematous sensitization. The drug is limited in its applicability in that it can only be used topically. Goldman et al<sup>43</sup> reported using tyrothricin in 1:5000 concentration on resistant skin infections in eleven patients. There were no signs of irritation. The use of the drug in rhinology and surgery was likewise encouraging. However, Otenasek and Fairman<sup>77</sup> reported two cases in which chemical meningitis developed after the frontal sinuses had been irrigated with a tyrothricin solution. Darling and Baumeister<sup>25</sup> treated 250 patients with nose drops containing tyrothricin suspended in a synthetic vasoconstrictor solution. Untoward effects were not mentioned.

### SULFONAMIDES

The sulfonamide drugs were all but forgotten in the wave of enthusiasm which accompanied the introduction of the antibiotics. Fortunately, investigation and study of these compounds has continued. In the face of ever-increasing organism resistance to the antibiotics, especially penicillin, these drugs are again assuming an important place in the physician's armamentarium. In fact, there is now an impression abroad (not statistically proven) that one of the sulfonamides (sulfamcrazine) is more effective than penicillin in the treatment of pneumonia.<sup>54</sup> In accepting the partial comeback of the sulfonamides, we must not overlook the costly lesson of the past nor accept isolated reports of low toxicity without reserve. Carver and Yonkman<sup>16</sup> reported on the use of 2.5 per cent sulfathiazole in propylene glycol as a mucus membrane spray in upper respiratory infections. Of "several score" patients treated there was no evidence of sensitization. Ballenger<sup>4</sup> found only seven instances of sensitization among 1,500 patients who received an average of 2.5 insufflations of powdered sulfonamide compounds for acute infections of the nose and throat. Clark<sup>18</sup> was favorably impressed with the local use of a 1 per cent solution of Sulfamylon (para-[amino-ethyl]-benzene sulfonamide hydrochloride) in surgical eye cases. In eighty-four cases treated there were no toxic reactions. Fox<sup>10</sup> used Sulfamylon as a spray in more than 200 cases of rhinosinusitis in 137 patients. No case of drug sensitivity was encountered, even though a number of patients used the drug on several occasions when they suffered repeated attacks of acute sinusitis.

Burger<sup>14</sup> recorded an interesting case of a soldier who developed edema of the face and hands, pruritus, erythema, and vesicle formation about the lips and chin on two occasions after oral ingestion of sulfathiazole. Later, when a sulfathiazole ointment was used as a venereal prophylactic, all the previously affected areas erupted but not the genitals. This case demonstrates that after sensitization to a sulfonamide occurs once, later exposure to the same drug can produce identical reactions whether the drug is taken orally or applied locally.

A new sulfonamide, 3, 4 dimethyl-5-sulfanilamido-isoxazole, has proved to be effective against *E. coli* and *Proteus vulgaris*. Narins<sup>73</sup> observed toxic symptoms in four of fifty patients treated with full therapeutic doses. Two patients developed dermatitis and two experienced nausea.

Studies on sensitivity to topically applied sulfonamides have proved enlightening. Sulzberger et al<sup>102</sup> made a study of 254 volunteers who were divided into four groups. Each group was treated with a cream containing one of four sulfonamides. These creams were repeatedly applied in the treatment of experimental standard



thermal burns on both arms. The results were as follows: Of forty-nine men treated with 5 per cent sodium sulfadiazine cream, 57 per cent developed a dermatitis. Of fifty-four men treated with 5 per cent sulfanilamide cream, 22 per cent developed a dermatitis. Of seventy-two men treated with 5 per cent sulfathiazole cream, 7 per cent developed a dermatitis. Of seventy-nine men treated with 5 per cent sulfadiazine cream, 5 per cent developed a dermatitis. In 48 per cent of the cases which developed dermatitis, the eruption appeared within two to eight days after the commencement of the local application. Only in the sodium sulfadiazine series did there seem to be a significant direct relationship between the number of applications and the incidence of dermatitis. Perhaps the size of the exposed area was also a factor here. Once a man developed a clinical sensitization dermatitis, he could not be treated again with the same sulfonamide without again developing a dermatitis. Only 31 per cent of the men who developed dermatitis subsequently showed a positive patch test with the offending sulfonamide. However, the patch test was positive in all cases who had a severe dermatitis. Of twelve men who developed dermatitis after topical application of sulfonamide cream, eight developed dermatitis and one, general symptoms and itching, upon the subsequent oral administration of 6.0 gm. of sulfadiazine. Of thirty-one men who received repeated applications of sulfonamide cream but who did not develop a dermatitis, five suffered from general symptoms but no dermatitis when later given 6.0 gm. of sulfadiazine orally. Of thirteen controlled subjects who had had no known previous exposure to sulfonamide, none developed dermatitis or general symptoms from the same oral dose of sulfadiazine. Apparently the sensitizing potential of various sulfonamides, when applied topically, corresponds directly to their solubility in water. Sodium sulfadiazine was a frequent offender, sulfanilamide was next, then sulfathiazole, and lastly sulfadiazine. The incidence of sensitization by externally applied sulfonamide is directly proportional to the preceding superficial skin damage at the site of application. Previous exposures to, and/or skin sensitization by, externally applied sulfonamide materially increases the risk of cutaneous and general reaction on subsequent oral administration of the same or related drugs.

Gottschalk and Weiss<sup>46</sup> patch-tested over 200 subjects, using three different sulfonamide ointments. Ten days to two weeks later the same patients were again patch-tested with the same materials. It was found that the number of persons sensitized by the patch tests was small: 2.3 per cent were sensitized by a 5 per cent sulfadiazine ointment (base pH 7 to 7.5), 0.49 per cent were sensitized by a 5 per cent sulfathiazole ointment (base pH 7 to 7.5), and 0.0 per cent were sensitized by a 5 per cent sulfadiazine ointment (base pH 8.1). These investigators concluded that the sulfonamide drugs are not highly potent cutaneous sensitizers if applied to only a small area of the skin and if applied for a period of less than five days. They agreed with Sulzberger's group that the danger of sensitization is greatly increased when the drugs are applied to previously damaged skin.

Many attempts have been made to clarify the allergic mechanisms involved in sulfonamide sensitivity. Results have been inconstant. In patients with known sulfonamide sensitivity some have been able to demonstrate that sensitivity by one or more methods (patch, scratch, intradermal, or passive transfer) while others have failed. As pointed out above, Sulzberger and his group<sup>102</sup> were able to demonstrate sensitivity by patch test in only 31 per cent of subjects who were known to have a sulfonamide sensitivity. Several investigators<sup>96,111</sup> have recently proved by successful passive transfer tests the existence of circulating antibodies in two cases of sulfadiazine sensitization.

To the many eruptions already attributable to the sulfonamides Philpott<sup>80</sup> has added another. He has reported three cases in which a psoriasiform dermatitis appeared following the oral administration of one of the sulfonamide group. A clinical diagnosis of psoriasis was made in each case. This phenomenon has been discussed elsewhere,<sup>105</sup> and while generally acknowledged to occur, the pathogenesis remains obscure. Do the sulfonamides cause the eruption or is it simply an aftermath of the condition (sore throat, et cetera) for which the sulfonamide was originally prescribed?

#### THE ANTIHISTAMINICS

These drugs are considered here solely from the standpoint of their side effects and toxicity. The side effects of Benadryl and Pyribenzamine are well known and are listed merely for the sake of completeness. Those of Benadryl include drowsiness, dizziness, weakness, dryness of mouth, nausea, nervousness, confusion, poor co-ordination and gastrointestinal complaints.<sup>76</sup> Those of Pyribenzamine include chiefly sedation and gastrointestinal disturbances such as nausea, bad taste in the mouth, anorexia, heartburn, epigastric distress, abdominal cramps, and



occasionally vomiting and diarrhea.<sup>62</sup> Loveless,<sup>63</sup> in a comparative study, noted sedation in 61 per cent of her patients taking Benadryl while only 20 per cent of patients on Pyribenzamine manifested this symptom. O'Leary and Farber<sup>76</sup> observed side reactions in 31 per cent of patients taking Benadryl. As a rule, these side effects are not of a serious nature, and with continued administration a "tolerance" may be established.<sup>67</sup> However, a number of unusual reactions have been reported in the literature of the past year. Steinberg<sup>69</sup> reported hysteria of a severe degree occurring in a patient taking 350 mg. of Benadryl daily for control of hay fever symptoms. When the drug was discontinued, normalcy was regained within forty-eight hours. Weil<sup>110</sup> reported an epileptiform seizure in a three-and-a-half-year-old boy following ingestion of 100 mg. of Benadryl. Of course, this dose was considerably in excess of the recommended daily dose of 2 mg. per pound of body weight. Geiger et al<sup>41</sup> reported a shock-like reaction occurring in a twenty-five-year-old woman. This patient took 50 mg. of Benadryl t.i.d. After a total dose of 300 mg. had been reached she experienced palpitation, dimmed vision, malaise, and nausea. Following another 50 mg. dose she was found in bed, cold, pale and pulseless. Complete recovery was attained in three hours following administration of epinephrine. Later Benadryl again produced the same symptoms. A prolonged reaction to Benadryl was observed by Schwartzberg and Willerson.<sup>95</sup> An adult man took twenty-three 50 mg. capsules of Benadryl over a twenty-day period. Ingestion of the drug was irregular, but the patient never took more than three capsules on any one day. Progressive symptoms (intensifications of ordinary side reactions) appeared after one week. When the medication was stopped, recovery was slow. At the end of a three-month period practically all toxic symptoms had subsided. Barksdale and Hall<sup>8</sup> observed the development of a skin eruption in two patients on Benadryl. They suggested that the Benadryl may have been responsible, but further proof was lacking. The same authors observed three patients who possibly exhibited withdrawal symptoms when they became nauseated on stopping the drug.

Brown and Crepea<sup>12</sup> described a case in which asthma developed following ingestion of Pyribenzamine tablets. Investigation revealed that the patient was sensitive to the gum tragacanth used in compounding the tablets. This case very nicely demonstrates that other constituents should be investigated before ascribing sensitivity reactions to the main ingredient of a medication. Two reports have appeared of eruptions occurring in the wake of Pyribenzamine administration. Epstein<sup>33</sup> has described two cases. The first case suffered from a chronic atopic eczema. An erythematous macular eruption, following the lines of body cleavage, appeared on the arms, legs, and trunk within twelve hours after oral ingestion of Pyribenzamine. This dermatosis resembled pityriasis rosea. After the drug was discontinued, the lesions disappeared and reappeared when Pyribenzamine therapy was resumed. The second case also had a chronic eczema. Pyribenzamine was administered, and less than ten hours later, papular erythematous lesions appeared and spread rapidly over the whole body. Two weeks later the eruption disappeared, and the original eczematous lesions remained. Additional history revealed that another physician had prescribed the same medication two months before. The ingestion of one tablet had caused an immediate generalized eruption of the same type. Harris and Shure<sup>19</sup> reported a case of a woman who developed a vesicular eczematoid eruption while taking Pyribenzamine. There was no previous history of dermatitis. After subsidence of the eruption Pyribenzamine tablets were given a second and third time in disguised form. Each time the eruption was reproduced. This patient had taken many medications in the past, including aspirin, various headache tablets, laxatives and vitamin pills without untoward reactions. Therefore, the authors felt that her sensitivity was due to Pyribenzamine and not to another ingredient used in compounding the pills. Unfortunately in none of the three reported cases of dermatitis was a trial made with chemically pure Pyribenzamine.

Granulocytopenia probably due to Pyribenzamine has been reported by Blanton and Owens.<sup>11</sup>

Apparently there are no contraindications to the use of the antihistaminics during pregnancy.<sup>86</sup>

#### BAL (2,3-DIMERCAPTOPROPANOL, BRITISH ANTI-LEWISITE

Very favorable reports on the use of BAL in heavy metal poisoning continue to appear in the literature.<sup>10,19,26,57,61,66,90,91,94</sup> Reeve<sup>91</sup> has called this useful drug "the answer to the syphilologist's prayer" because it has relieved the dread of arsenical reactions. The internist might also rejoice over the effectiveness of BAL in combating the toxic effects of gold arising during treatment of rheumatoid arthritis. The need for such an agent becomes apparent in the light of a recent report by

Browning et al<sup>13</sup> on gold therapy in forty-seven patients with rheumatoid arthritis. A high incidence of toxic reactions to gold was noted, 62 per cent of the patients being involved. Although most of these reactions were of little consequence, there were two cases of exfoliative dermatitis, with one death. Stomatitis,<sup>19,66</sup> anal ulceration,<sup>66</sup> exfoliative dermatitis,<sup>10,26,66</sup> pruritus,<sup>10,26,66</sup> thrombocytopenic purpura,<sup>61</sup> granulocytopenia,<sup>61</sup> and conjunctivitis,<sup>19,66</sup> each a toxic sequela of chrysotherapy, have responded to BAL. To be effective in combating reactions the drug must be used early, at least within two months from the onset of toxic symptoms,<sup>87,88,90</sup> although treatment of exfoliative dermatitis even after this length of time may afford some amelioration of symptoms.<sup>66</sup> There are indications that BAL may be of value in the management of lead poisoning.<sup>103</sup> It is useless in the treatment of argyria.<sup>85</sup>

Unfortunately, BAL has a toxicity of its own. Among its side effects are malaise, nausea, vomiting, burning of the skin, burning sensation of the gums, nose, and eyes, excessive salivation, lacrimation, paresthesia, perspiration, sense of warmth, pain in the legs, arms, abdomen, and head.<sup>106</sup> Cohen et al<sup>10</sup> reported such symptoms of BAL intoxication in three of six patients treated. These symptoms are, as a rule, transient and may be disregarded in view of the benefit obtained. Tye and Siegel<sup>106</sup> gave ephedrine sulfate to a patient in whom BAL caused symptoms similar to a serum sensitivity reaction and succeeded in alleviating the discomfort. A second patient with toxic symptoms from BAL likewise responded. These authors pointed out that the preparation of the patient with ephedrine sulfate (25 mg.) shortly before the injection of BAL may lessen the intensity or prevent entirely the side effects of this valuable remedy. Green and Russell<sup>88</sup> claim that the symptoms of toxicity to BAL can be explained on the basis of tetany due to depletion or unavailability of calcium or magnesium or both.

Sulzberger, Baer, and Kanof<sup>101</sup> reported their experiments with BAL containing preparations applied to the skin of rabbits and human beings in a study of comparative effectiveness in decontamination, treatment and protection against damage by lewisite and other arsenical vesicants. They found that when a 5 per cent concentration of BAL was employed, the vehicle in which the drug was incorporated did not appear to exert a great influence on the decontamination and therapeutic efficacy of BAL. However, the protective efficacy of the BAL was greatly influenced by the vehicle in which it was contained. On the basis of their findings and recommendations, relatively stable and effective BAL preparations were made available to our armed forces during the recent war.

Cornbleet<sup>22</sup> recorded his observations and findings of his personal sensitization to BAL. The dermatitis appeared on the regions of the hands used in grasping a syringe. A 1 per cent concentration of BAL in peanut oil gave a positive patch reaction. His attempts to demonstrate cross sensitivity to related compounds are discussed elsewhere in this review.

#### 5-NITRO-2-FURALDEHYDE: SEMICARBAZONE (FURACIN)

This is one of a series of chemicals known as the "furans" which are derived from oat bran. It is both bacteriostatic and bacteriocidal and has been shown to be effective in the local control of both Gram-positive and Gram-negative organisms. The original report on the use of this substance in dermatology by Downing, Hanson, and Lamb<sup>27</sup> was enthusiastic, but the high incidence of sensitization to the drug (3 per cent) could not be entirely overlooked. The Council on Pharmacy and Chemistry<sup>23</sup> advised caution in using the drug for a period longer than five days because of the danger of sensitization. There is a possibility that the water-soluble base in which the substance is incorporated may be responsible in part for the sensitization reactions so far reported. Further investigation along these lines is indicated. At any rate, before Furacin dressings can come into general use, the hazard of sensitization must somehow be reduced.<sup>31</sup> Morin<sup>71</sup> reported a moderate case of sensitization to Furacin after six weeks' use of the medication. An erythematous-vesicular eruption appeared at a graft site which was being treated with Furacin and also at a donor site which was healed but which had previously been treated with the drug. Hill and Flood<sup>51</sup> have reported a psoriasiform eruption appearing twenty-four hours after the use of a Furacin ointment. Although patch tests were negative, these authors held the drug responsible. The eruption subsided uneventfully in ten days.

#### BISTRIMATE (SODIUM BISMUTH TRIGLYCOLLAMATE)

It was generally thought that the search for a satisfactory oral bismuth preparation was completed when Sobisminol was introduced in 1939. However, it was soon realized that gastrointestinal disturbances were frequent with the use of this

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drug, and it fell into disuse. The next and latest oral bismuth compound to be introduced is Bistrimate (Sodium Bismuth Triglycollamate). This compound contains 18.3 per cent bismuth and is readily soluble in water. Lehman and Fassett<sup>59</sup> have reported extensively on the experimental use of the drug in mice, rabbits, and dogs to determine its level of toxicity and other factors. Bistrimate was then used on fifteen test subjects. It was determined that a potentially effective urinary excretion level could usually be maintained at a dosage which was well tolerated over extended periods. In two cases the drug had to be discontinued because of anorexia. Otherwise there were no evidences of toxicity. Five patients with syphilis, when treated with the new drug, showed the typical response of the effects of bismuth therapy. The authors concluded that Bistrimate affords a safe and convenient means of administration where bismuth is indicated. Sawicky<sup>63</sup> reported treating thirty cases of lupus erythematosus with this drug in doses of one to two tablets (75-150 mg. of metallic bismuth) three times a day. Some patients received the drug for as long as twenty-six weeks. Treatment had to be stopped in two cases who developed stomatitis with trigeminal neuralgia. Two other patients developed stomatitis but were able to continue on reduced dosage. One patient developed muscular pain in all four extremities, but after a two-week rest period he resumed treatment without ill effect. Blood and urine studies in all patients showed no significant aberrations.

### QUINACRINE HYDROCHLORIDE (ATABRINE)

Occasional reports on dermatitis due to atabrine continue to appear in the literature.<sup>7,75</sup> Nisbet<sup>75</sup> has comprehensively reviewed the subject in the light of his personal experience and also the voluminous literature on the subject. Atabrine principally produces three main types of cutaneous reactions. The eczematoid type is the most common reaction and accounts for about 80 per cent of cases of dermatitis from the drug. This is a chronic, dry or exudative, symmetric eruption occurring most frequently about the ears, eyelids, periorbital region, the dorsa of the hands and feet, and those areas most often affected by seborrheic dermatitis. The second type is lichenoid and constitutes about 12 per cent of patients affected. This type resembles lichen planus although it is more widespread. This has been the most publicized form of atabrine dermatitis. The third type of reaction is exfoliative dermatitis similar to that produced by arsenicals. It may be a primary reaction or secondary to the lichenoid or eczematoid types. Other untoward reactions include hepatic damage, visual disturbance, and psychosis. Barker<sup>7</sup> reported a case of hyperkeratosis of the palms and soles which he believed was caused by atabrine ingestion.

### MISCELLANEOUS DRUG ERUPTIONS

Five cases are reported by Watson et al<sup>100</sup> in which purpura followed the administration of stilbesterol or other estrogenic substances. The clinical symptoms were accompanied by a marked decrease in the platelet count. In the majority of the cases the estrogens had been administered over a prolonged period. The authors were guarded in their conclusions. They simply suggested that allergy to estrogens may be a factor in purpura inasmuch as there are a number of reports on the association of purpura with menstruation.

Fourteen patients, of whom thirteen were female, were studied by Bauer et al<sup>9</sup> following reactions after intramuscular injections of pork liver extract. These patients were found to be sensitive to pork, the sensitivity being species-specific rather than organ-specific. The most common reaction was urticaria with pruritus and edema of the face and lips. The second general type of reaction was manifested by cyanosis, perspiration, thready pulse, weakness, and fainting. Local swelling, induration, and pruritus at the site of injection was a third type of reaction. All symptoms disappeared with change to beef or lamb extracts.

Lima<sup>60</sup> reported the case of a thirty-three-year-old nondiabetic person with an atopic history who became sensitized to crystalline insulin. The reaction consisted of a generalized urticaria. Ophthalmic, scratch, and intradermal tests with crystalline insulin and with beef and pork regular insulin were positive. The same tests elicited negative results with beef and pork pancreatic extracts and with 1 per cent amylopsin solution. It was possible to demonstrate serum reagins for only crystalline insulin. Leavitt and Gastineau<sup>58</sup> showed in two insulin-sensitive diabetic patients that it was possible to reduce the intensity of the reaction either by prior oral administration of Benadryl or by the addition of Benadryl in 1:1000 solution directly to the insulin in the syringe.

Melkon and Scheidell<sup>60</sup> reported eight episodes (in six patients) of constitutional

anaphylactic-like reactions following the injection of sclerosing solutions into varicose veins. Such reactions have been reported previously. The patients developed urticaria, were warm and weak with rapid pulse, low blood pressure, and puffy congested eyes. Two of the episodes were produced by quinine HCl and urethane. The remainder were equally divided between sodium morrhuate and Synscol. The symptoms were the same regardless of the inducing agent. The reviewers have recently seen a case demonstrating such a reaction following repeated injection of sodium morrhuate into varicose veins. Recovery was complete in about half an hour following injection of 0.5 c.c. of 1:1000 adrenaline subcutaneously.

A case of exfoliative dermatitis due to codeine sensitivity has been reported by Moyer.<sup>72</sup> Drug eruptions due to codeine are extremely rare. Only twelve cases have previously been reported.

Rowe and Rowe<sup>92</sup> reported four cases of local necrosis (Arthus phenomenon) due to cutaneous allergy to extracted epinephrine. Three of the four patients subsequently used synthetic epinephrine without local reactions.

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## RABIES VACCINE (ULTRAVIOLET IRRADIATION KILLED)

Brains of rabbits paralyzed by infection with fixed rabies virus are harvested, emulsified and brought to a 10 per cent by weight suspension of tissue in isotonic solution of sodium chloride and filtered through sterile bolting silk. Following filtration, the tissue suspension in a continuously flowing thin film is exposed to the germicidal rays of ultraviolet lamp. Preserved with sodium ethyl mercuri thiosalicylate 1:10,000. Rabies Vaccine (Ultraviolet Irradiation Killed) is employed for the prophylaxis of rabies.

Dosage.—I e.c. subcutaneously, daily for 14 to 21 days. For severe exposure-bites on face or adjacent to central nervous system, 21 doses, two daily for the first three to seven days and then one dose daily. (*J.A.M.A.*, 137: 1317, 1948)

# News Items

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## ALLERGY INSTRUCTIONAL TOURS

The Committee on Extension of Postgraduate Education of the American College of Allergists (Chairman, Dr. Jonathan Forman) is attempting to arrange a series of instructional tours throughout the country. Each tour will consist of a number of cities which can be visited within a period of a week or two. Allergists in these cities will be asked to co-operate with the committee allowing themselves to be visited by out-of-town men for teaching purposes, not in the sense of formal undergraduate instruction but to enable the visitors to pick up what information they can. While the visitors will for the most part be practitioners who are not full-time allergists, there is no reason why allergists themselves should not take advantage of this program so as to allow for a mutually beneficial exchange of ideas and experiences.

Some allergists throughout the country have already been queried on the subject and almost without exception have agreed to take part in the program. A well-known laboratory on the West Coast has offered to participate by showing visitors techniques of pollen collection and extraction and specimens of the local flora, not only from their herbarium but also by visits to the field and to the pollen shed.

Present plans call for a central registry where a list of participants in this program will be kept and where itineraries will be planned for applicants. After the latter indicate which cities and which men they wish to visit, the allergists to be visited will be notified in advance as to who will visit them and when.

Fears of being flooded with tourists have been expressed by some men. The committee realizes the inconveniences accompanying intrusion on office or clinic time, and every effort will be made to minimize this. In the first place, the number of visitors seen by any one man will be sharply restricted to no more than possibly three or four a year, to begin with. Secondly, the time of stay will generally be no longer than one afternoon, possibly two. Thirdly, the qualifications of each applicant and the time of his visit will be sent to the co-operating allergist in advance. Should circumstances so dictate, the allergist will then have the opportunity of notifying the central bureau of his inability to accept the applicant, and the visitor will consequently not be routed to him. On the other hand, unless such occasions are truly exceptional, the purpose of the program could be easily negated, so that obviously only those physicians should take part in this program who are willing and able to accept the entailed burdens.

Preliminary response to the project has been heartening, and the Committee now desires to expand the scope of its plans. The co-operation of any member of either College or Academy, who desires to participate under the conditions outlined above, is invited. Also invited is the co-operation of dermatologists and ENT men who would be interested in furthering this program. All such physicians who have not been queried up to now and who clearly understand the potential demands which may be made upon their time are urged to send their schedule of office and clinic hours (together with comments on special and general facilities, if desired) to Dr. A. M. Targow, 6333 Wilshire Boulevard, Los Angeles 36, California.

## COURSE IN CLINICAL ALLERGY

Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York, announces a course in Clinical Allergy under Dr. Robert A. Cooke and his staff at Roosevelt Hospital from November 8 through 20, 1948.

This course is designed to provide internists, pediatricians, and other physicians a review of modern concepts of the theoretical and practical aspects of allergy, in relation to clinical problems. All types of allergic disease will be studied including the less common vascular and cerebral allergies. The practical work will include history taking, physical examination, skin testing by direct and passive transfer methods, and laboratory diagnosis. In the laboratory the principles of allergic extractions and standardizations will be considered in a practical way and the preparation of individual extracts. There will also be demonstrations of anaphylaxis, Dale reactions, precipitin tests and preparation of autogenous vaccines. Maximum class, 8; minimum 6.

Those desiring to take this Course should write to Dr. John B. Truslow, Assistant Dean, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32, New York.

## PITTSBURGH ALLERGY SOCIETY

At the May meeting of the society the following program was presented:

1. A Report of the Pollen Commission—E. P. Claus, Ph.D., Chairman.
2. Streptomycin Sensitivity—Case report—J. A. Mansmann, M.D.
3. Kaposi's Varicelliform Eruption—Report of Two Cases—Irwin Solow, M.D. (guest).

## SWISS ALLERGY SOCIETY

Word has been received that next month a new Swiss Allergy Society is to be organized. The most outstanding commercial and research workers in Switzerland are already members of the International Association of Allergists and they will sign an appeal to form a Swiss organization.

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A copy of the Financial Report of the American College of Allergists for the year 1947 will be sent to any member of the College requesting it. Requests should be addressed to the Secretary-Treasurer, 423 La Salle Building, Minneapolis 2, Minnesota.

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Word has been received from Dr. Donald G. Anderson, Secretary of the Council on Medical Education and Hospitals, that through an oversight in his office the listing of the Postgraduate Course to be given by the American College of Allergists, November 8-12, 1948, was not included in the listings of the June 19 issue of *The Journal of the American Medical Association*, but that a News Item concerning this course will be included in an early issue of *The Journal*. Our instructional courses have been listed in the past under the Postgraduate Continuation Courses for Physicians compiled by the Council on Medical Education and Hospitals.

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Dr. Bernard N. Halpern, Paris, France, the Lauréat of the Institute and Académie of Medicine, Chief of Laboratories of the Faculté of Medicine and Chief of Research of the National Center of Scientific Research, is coming to America in September. Dr. Halpern is especially noted for his contributions on the antihistaminic drugs. He plans to visit Chicago, then the Mayo Clinic and return to New York where he will give two lectures at the Blumenthal Auditorium of the Mt. Sinai Hospital under the auspices of The American College of Allergists: On October 7, 8:30 p.m., "The Role of the Capillary Permeability in the Production of Acute Pulmonary Edema and the Action of the Synthetic Antihistaminic Substances in this Syndrome," and on October 14, 8:30 p.m., "Experimental and Clinical Researches on a New Series of Antihistaminic Substances Derived from Phenothiazine." All physicians interested, particularly allergists, are invited to attend these lectures.



## NEWS ITEMS

### QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY

Recently new appointments have been made to the Editorial Board of the *Quarterly Review of Allergy and Applied Immunology*. The Editorial Board now consists of Fred W. Wittich, M.D., Editor-In-Chief, Harold A. Abramson, M.D., Ethan Allan Brown, M.D., Stephan Epstein, M.D., Jerome Glaser, M.D., French K. Hansel, M.D., David Harley, M.D., Bayard T. Horton, M.D., Werner Jadassohn, M.D., Paul Kallos, M.D., A. Oliveira Lima, M.D., Harry C. Olislagers, M.D., Bret Ratner, M.D., G. Estrada de la Riva, M.D., Adolph Rostenberg, Jr., M.D., Guido Ruiz-Moreno, M.D., Prof. Dr. Piero Sangiorgi, Morris Scherago, D.V.M., Albert V. Stoesser, M.D., J. Warrick Thomas, M.D., and Alfred J. Weil, M.D.

### THE INTERNATIONAL ASSOCIATION OF ALLERGISTS

A full page advertisement will appear in *THE ANNALS* soon announcing the publication of the *International Archives of Allergy and Applied Immunology*, the official organ of the International Association of Allergists. The first issue will consist of a symposium on psychosomatic and neurologic allergy. The Editorial Board, composed of some of the most outstanding scientists throughout the world, will soon be completed.

Provisional plans have been made to hold the first International Congress at Zurich in October, 1949. Professor William Löffler of Zurich is Chairman of the Congress and Professor A. Grumbach of Zurich is the General Secretary. A tentative program has been arranged and the persons to be invited as reviewers and lecturers have been selected. Professor Rolf Meier of Basel, Switzerland, has invited the members of the International Association to spend at least one day of the Congress at Basel where the pharmacologic aspects of the allergic diseases will be discussed in connection with demonstrations by the large chemical industries there. A registration of at least 400 is anticipated.

### FORUM ON ALLERGY

A forum on Allergy will be held under the auspices of the Central Pennsylvania Allergy Society in the Luzerne County Medical Society Building, 130 South Franklin St., Wilkes-Barre, Pennsylvania, Thursday, October 14, 1948.

A business meeting and luncheon for members of the Society will be held at Hotel Sterling in the morning.

The afternoon program will include the following scientific papers, with discussion after each paper.

"Food Allergy"—ARTHUR C. KALISCH, M.D.

"The Treatment of Asthma from the Viewpoint of a General Practitioner"—HARRY L. ROGERS, M.D.

"Papular Urticaria"—JOHN P. SCULLY, M.D.

"The Present Status of Antihistamine Drugs"—MERLE M. MILLER, M.D.

"Office Management of the Allergic Child"—JEROME GLASER, M.D.

"Bronchoscopy as Applied to Allergy"—SAMUEL T. BUCKMAN, M.D.

Special exhibits will be on display. Following the scientific session dinner will be served in the Adams Room, Hotel Sterling, and will be open to physicians, members, wives and friends. Reservations should be made through the Secretary-Treasurer, Ralph M. Mulligan, M.D., 18 North Eleventh Street, Reading, Pennsylvania.

### DRUG FIRM AWARDED CITATION BY NAVY FOR WAR WORK

Award of a certificate of achievement to Winthrop Chemical Company, now Winthrop-Stearns, Inc., manufacturer of pharmaceuticals, was made July 15, 1948, by the Surgeon-General, U. S. Navy, in recognition of "Meritorious and outstanding services rendered to the Navy's Medical Department during World War II."

# IN MEMORIAM

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## CLARENCE K. WEIL, M.D., F.A.C.A.

As the *ANNALS OF ALLERGY* was going to press, we were shocked when receiving the sad news of the sudden death of Dr. Clarence K. Weil of Montgomery, Alabama, in May, 1948, at the age of forty-eight years. Dr. Weil was born May 16, 1900, in Montgomery. He was graduated from Starke's University School in 1916 and from the University of Alabama, receiving the degree of B.S., in 1919. He was graduated from Columbia University Medical School in 1923 and held an internship at Mt. Sinai Hospital in New York from 1923 to 1926.

Doctor Weil was an instructor of nurses at St. Margaret's Hospital in Montgomery. He was also an instructor of residents at St. Margaret's Hospital.

Doctor Weil was a member of Phi Beta Kappa and Alpha Omega Alpha honorary societies, and a member of The American Academy of Allergy and The American College of Allergists. He was also a member of the American College of Physicians and was certified by the American Board of Internal Medicine.

Doctor Weil, at the time of his death, was Chief of Staff of the Medical Service at St. Margaret's Hospital, and Chairman of the Hospitalization Committee. He belonged to the Montgomery County Medical Society and the Alabama State Medical Society. Doctor Weil served with distinction in both World War I and World War II with the rank of Lieutenant Colonel.

Doctor Weil made some valuable contributions to the field of medicine, and allergy in particular. He studied assiduously the local problems which may be factors in causing hay fever in Alabama. He published work on plants causing hay fever in Alabama, and he is particularly known for his article on "Summer Hay Fever of Unknown Origin in the Southeast," which appeared in the *Journal of Allergy*, May, 1940. He thus pioneered the recognition of the hay fever "x" problem in the South, which has been the subject of much investigation by himself and his colleagues.

Doctor Weil is survived by his wife, Dorothy, and two daughters, Mrs. Lee Rudlin and Miss Joan Weil.

The officers and members of the College extend their deepest sympathy to the immediate family.

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## OPPORTUNITY FOR JUNIOR FELLOW

A well-known allergist with an established allergy practice is desirous of adding to his staff a junior fellow to study and profit by the many cases of all types of allergic manifestations that pass through his private office and those encountered in the free clinics in which he is connected. The maximum compensation of \$150.00 a month would be available, providing the applicant would agree to stay a minimum of six months up to a maximum of one year. Application together with photograph and qualifications and recommendations from two or three recognized internists or allergists, should be addressed to The American College of Allergists, 423 La Salle Medical Bldg., Minneapolis 2, Minnesota.

# A Post-Convention Suggestion

The May-June issue of the ANNALS OF ALLERGY featured a trip over the Northern Pacific Railway through Minnesota, North Dakota, Montana, Idaho, and Washington for those planning to attend the American College of Allergists Instructional Course to be held in Portland, Oregon, November 8 to 12, 1948. Supplementing this suggestion, we are pleased to show below a suggested return itinerary including a side trip via steamer from Seattle to Victoria and sight-seeing trips in these interesting seaports.

Lv. Portland—Nor. Pac. Ry	11:30 PM	Nov. 8
Ar. Seattle—Nor. Pac. Ry.	6:30 AM	Nov. 9
Lv. Seattle—Can. Pac. Steamer	7:50 AM	Nov. 9
Ar. Victoria—Can. Pac. Steamer	12:50 PM	Nov. 9
Tour this very interesting Canadian Capital City and the exotic Butchart's Gardens.		
Lv. Victoria—Can. Pac. Steamer	4:30 PM	Nov. 9
Ar. Seattle—Can. Pac. Steamer	9:30 PM	Nov. 9
Overnight in Seattle.		
Open Forenoon.		
2:00 PM—Tour business, financial, residential and University districts of this interesting city and seaport. Two full hours of comprehensive sightseeing.		
Lv. Seattle—North Coast Limited	10:45 PM	Nov. 10
Spokane—North Coast Limited	8:15 AM	Nov. 11
Lake Pend Oreille, Cabinet Gorge and Mission Range.		
Missoula	3:35 PM	Nov. 11
Hell Gate Canyon.		
Butte	6:20 PM	Nov. 11
Biggest mining camp on earth, Continental Divide, Bozeman Pass.		
Livingston	10:25 PM	Nov. 11
Absaraka Mountains and Yellowstone River.		
Bismarck	12:20 PM	Nov. 12
Capital of North Dakota, Missouri River, Red River Valley—Breadbasket of the world.		
Fargo		
Minnesota—Land of 10,000 Lakes		
Minneapolis	9:27 PM	Nov. 12
St. Paul	10:00 PM	Nov. 12
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\*Levin, S. J., and Mass, S. S.: Clinical Results with Hydryllin in Asthma and Hay Fever, to be published.

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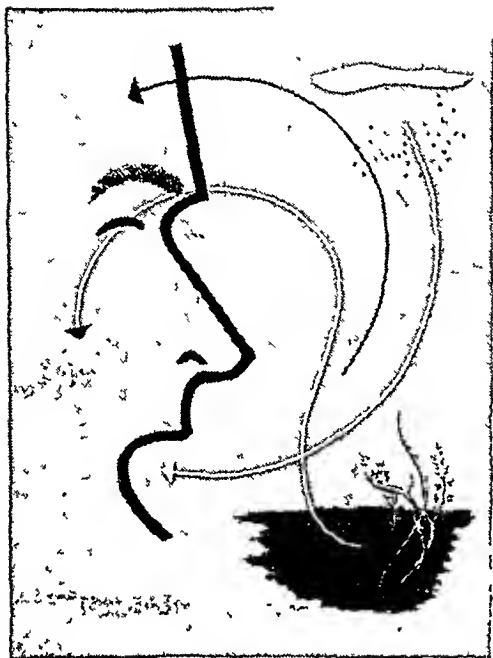
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1. Brown, E. A., et al. The clinical evaluation of a new histamine antagonist "Decapryn," *Ann. Allergy* 6:1-6 (1948).
2. Feinberg, S. M., et al. A new antihistaminic drug (Decapryn), *J. Lab. & Clin. Med.* 33:319-324 (1948).
3. Sheldon, J. M., et al. Clinical observations with Decapryn, a new antihistaminic compound, *Univ. Mich. Hosp. Bull.* 14:13-15 (1948).
4. MacQuiddy, E. L. Personal communication.

Decapryn (brand of Doxylamine) Succinate 25 mg. scored tablets—available at prescription and hospital pharmacies in 100's and 1000's.

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XXIV





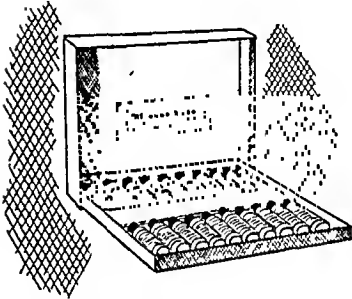
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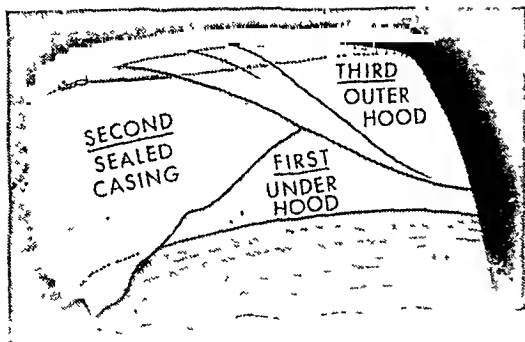


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*for the Patient*  
*Suffering from...*



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 HAY FEVER - URTICARIA**

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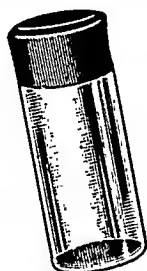
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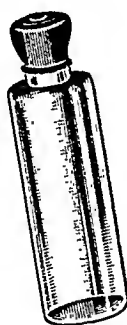
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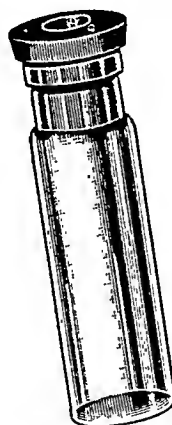
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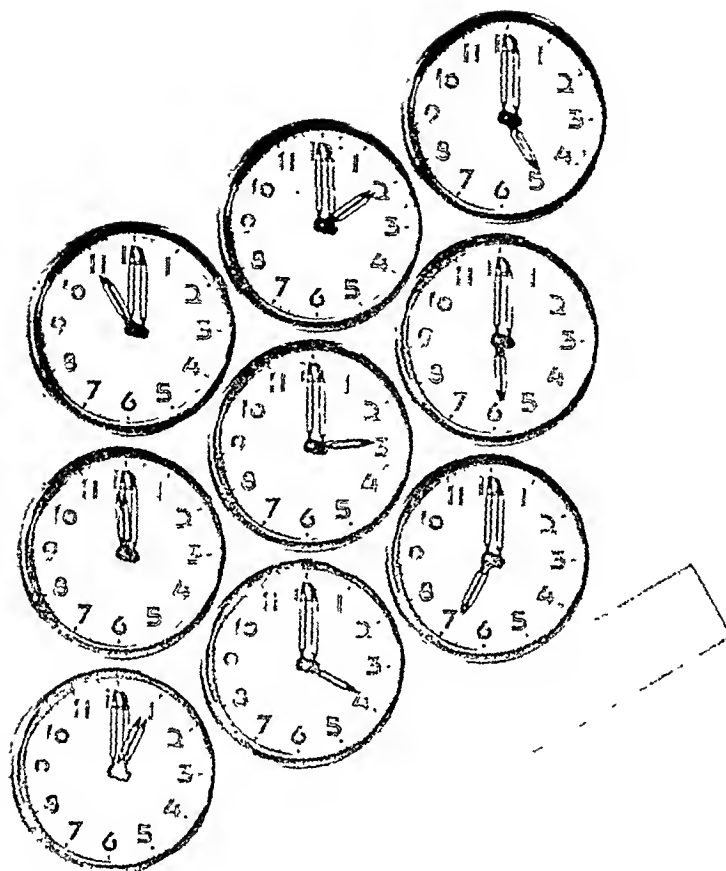
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when public allergy  
number 1 is

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**REFERENCES**

1. Jones, B. B: Virginia Med. Monthly, 74:241, June, 1947.
2. Levine, S. Z: J. A. M. A., 128:283, May 26, 1945.
3. Schroeder, L. J. et al: J. Nutrition, 32:413, Oct., 1946.

# ANNALS of ALLERGY

Official Journal of the American College of Allergists

Editorial Office  
634 North Grand Boulevard  
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Executive Office  
423 La Salle Medical Bldg.  
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**Annals of Allergy** is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, a current bibliography, editorials, case reports, new suggestions, questions and answers, news items and matters concerning the affairs of the American College of Allergists.

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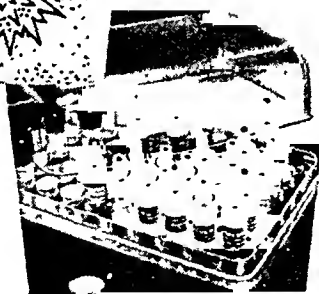
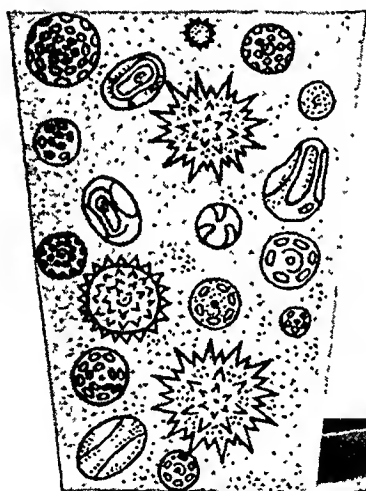
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Volume 6

May-June, 1948

Number 3

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## PSYCHODYNAMICS AND THE ALLERGIC PATIENT

HAROLD A. ABRAMSON, M.D., F.A.C.A.  
New York, New York

IT has been known from ancient times that attacks of asthma could be precipitated by situations engendering anger and other emotional responses. Similarly, hay fever and certain dermatological conditions were recognized as being markedly affected by and perhaps even initiated by psychological forces. However, the influence of Virchow and Pasteur formulated a new morphological and mechanical era in medical thought.<sup>4, 6, 11</sup> This era was coupled with the rise of laboratory techniques of great precision, leading to a new immunology based upon physical and chemical principles. Incidental to this development of physicochemical influence, the role of emotional factors in the allergies was forced into the background to the extent that until the last few years none of the standard American books on allergy seriously considered these factors in a systematic way.

### PRESENT RELATIONSHIP OF ALLERGY TO PSYCHOSOMATIC MEDICINE

Let us examine two medical journals, one devoted to psychosomatic medicine and the other devoted to allergy in the period from 1939 to 1946. During this period in the journal, *Psychosomatic Medicine*, there were published twenty papers relating specifically to emotional problems in the allergic state.<sup>10</sup> In the only American journal devoted to clinical allergy, published during the same period, there was only one brief report on the same topic. Surely this lack of communication between those interested in the solution of medical problems by psychosomatic techniques and those resting mainly on immunologic techniques is not desirable. In all fairness, not only have the allergists largely

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From the First Medical Service and the Laboratories of the Mount Sinai Hospital, New York City.

This research has been aided in part by grants from the Josiah Macy, Jr., Foundation, New York City, and the Foundation for Research in Pulmonary Disease, New York.

neglected certain important aspects of psychosomatic medicine, but the psychiatrists also, too often, are apt to neglect the massive structure of immunologic data which I have just touched upon. Why hasn't better rapport between the immunologic and psychologic techniques in medical practice been satisfactorily established?

#### THE A PRIORI FAILURE OF THE MODEL IN CLINICAL PRACTICE

For someone who has mainly published data on physicochemical mechanisms connected with immunologic processes in allergy to venture to give a paper on, "Psychodynamics and the Allergic Patient," might first be construed as a startling shift from a well-defined path of basic research. However, this is an assumption which frequently did not harmonize with my experience in the clinical practice of allergy during the last decade. This exploration of the utilization of psychodynamics in the practice of allergy is planned to determine through discussion what the allergist may expect in therapy from recent developments in the basic science of psychodynamics.<sup>11</sup> No matter how deeply our research in the fields of physics and chemistry takes us in attempts to provide models which explain the nature of immunologic and allergic processes, none of the models can ever *a priori* fully satisfy the physician in his daily therapeutic procedures, because none of these models ever completely reflects the complex pattern of the allergic individual.

The evolution of allergy as a clinical specialty depended upon progress and success in the correlation of anaphylactic data obtained from animals and man, with what was simultaneously discovered in the physics and chemistry of immunologic reactions.<sup>3</sup> New concepts, therefore, developed through proper observations of clinical manifestations of the tissue responses of man and animals, correlated with experiments like those of Obermayer and Pick, of Landsteiner<sup>7</sup> and his school, and of many others on the following:

1. The serologic specificity of proteins.
2. Cell antigens.
3. The nature and the specificity of antibodies.
4. The mechanism of sensitization by artificially conjugated antigens.
5. The mechanism of serologic reactions to simple chemical compounds.
6. Chemical investigation of nonprotein substances reacting specifically.
7. The mechanisms of antigen-antibody reactions in general.

In this attempt to relate chemistry and physics to immunology and to allergy, the experimenter, therefore, was, in the first place, always confronted with two questions: (1) What molecules are involved? (2) How do these molecules react as allergens to produce sensitizing antibodies which react specifically?

THE EXTENSION OF THE IMMUNOLOGIC MODEL TO A UNITARIAN THEORY: THE HISTAMINE THEORY AND ITS MANIFEST INADEQUACY

There was thus built up in the last half century a great field of physics and chemistry applied to immunology and allergy. These applications of the study of small and large molecules to clinical sensitization in man provided us with an extraordinarily useful technique in studying and treating the many clinical entities comprising the subject of allergy. The importance of this immunologic model for most of the clinical manifestations of allergy cannot be overestimated. Indeed, it has created the specialty of allergy. The drive for simplification by means of simple models led directly to a unitarian mechanism designed to account for all of the allergic patterns: The current histamine theory of allergy.\* There is no doubt that histamine, which is a low molecular weight imidazole, does reproduce, to a certain extent, some of the manifestations connected with allergic reactions. Thus the wheal produced by histamine and the wheal produced by an allergen-antibody reaction are very similar. However, all skin reactions and even all wheals connected with the allergic state are not similar to those produced by histamine. Nor can the whealing responses to physical agents like light and cold be explained without eliminating the basic feature of the histamine theory: the rapid diffusibility of the histamine molecule. Indeed, I could use the entire space allotted to me describing how this histamine model, often used to explain conveniently almost every clinical and experimental entity of allergy, has been unjustifiably utilized.

What is the difficulty which prevents those who utilize physico-chemical models from incorporating into their thinking and clinical utilization the rapidly growing science of psychodynamics? Is this desire to utilize models a characteristic of the growth of science in general, or is it something limited to the evolution of medical practice? I shall demonstrate that the use of models is a part of the development of science.

\*There have been many reviews purporting to show the importance of histamine in the production of clinical syndromes of allergy and in the production of anaphylaxis. However, all of these reviews, with few exceptions, are biased in favor of the theory, and evidence contrary to the theory is deliberately omitted. An exception is to be found in the excellent review by J. H. Latner in his book, *Allergy, Anaphylaxis and Immunotherapy* (New York, 1943). In addition, the reader should consult Abramson, "The Histamine Theory of Allergy," *The Nervous Child*, 7:86, 1948, where the evidence contrary to the histamine theory is also presented in an integrated form.

## PSYCHODYNAMICS—ABRAMSON

### KELVINISM: FAILURE OF THE MODEL IN PHYSICS TO ACCOUNT FOR ALL PHYSICAL PHENOMENA

In 1932 the state of physics was in some ways analagous to the relationship of allergy with psychodynamics. The new experimental facts of relativity and quantum phenomena met with what can be termed an explanatory crisis.<sup>2</sup> Old ideas of mechanics and electrodynamics failed to explain the behavior of matter and of energy. The models which had been built up and had been utilized for many years were inadequate to account for the experimental facts of relativity and of radiation. Bridgman at that time pointed out that this crisis which confronted the physicist was only a repetition of what had occurred many times in the past. He mentions that similar crises confronted Prometheus when he discovered fire, and the first man who observed a straw sticking to a piece of rubbed amber or a suspended stone seeking the north star. Every kitten is confronted with such a crisis at the end of nine days. Whenever experience takes us into new or unfamiliar realms a new crisis of some type must develop. To quote Bridgman: "Now what are we to do in such a crisis? It seems to me that the only sensible course is to do exactly what the kitten does; namely, to wait until we have amassed so much experience of the new kind that it is perfectly familiar to us and then to resume the process of explanation with elements from our new experience included in our list of axioms." Even though physical models are the favorite of the physicists, the temporary and ultimately inadequate character of attempted physical explanations based upon models alone is brought out by the successes as well as the failures of Lord Kelvin to find a mechanical explanation for all physical phenomena. To quote from Lord Kelvin: "I never satisfy myself until I can make a mechanical model of a thing. If I can make a mechanical model, I can understand it. As long as I cannot make a mechanical model all the way through, I cannot understand it. But I want to understand light as well as I can, without introducing things that we understand even less of."

### ANALOGY OF PROGRESS IN CLINICAL ALLERGY WITH PROGRESS IN PHYSICS

Just as the physicist was confronted with inexplicable facts about a score of years ago, so the allergist today frequently is confronted with phenomena not completely explained by the immunologic model which forms the basis of his specialty. In other words, one might say that in the study of certain cases classified as allergic, an explanatory crisis exists in the specialty of allergy similar to that which occurred in the much simpler science of physics in the 1930's. This situation in physics ultimately led

the physicist to incorporate into his thinking new theories having to do with relativity and radiation phenomena. New theories and new mechanisms do not ever clarify all of the unsolved problems. However, when the allergist consciously incorporates into his thinking the science of psychodynamics, even greater progress in the use of the immunologic model may be expected, because the incorporation of new ideas in science seems to stimulate further developments along classical lines. I shall shortly present some case records to illustrate how the immunologic or the classical model does not always completely account for the clinical syndromes in two groups of patients: (1) patients in whom allergy (immunologic basis) is present; (2) patients in whom the immunologic model cannot be demonstrated unequivocally in the light of present knowledge. Before presenting these case histories, let us define psychodynamics in more explicit terms.

#### PSYCHODYNAMICS AND PSYCHOMOTIVE FORCES

As you know, statics treats of the action of forces on bodies, the forces being arranged so that the bodies are at rest. The science which treats the action of forces on bodies in motion is called dynamics. It is convenient to say that the science which treats the action of psychological forces on behavior may properly be called the science of psychodynamics. The word behavior, as used here, includes the unit manifestations of the clinical syndromes of the allergies, such as the type of respiration, the response to skin stimuli, reactions of the patient to sensitizing antigens, or patterns analogous to those just indicated.

Rado<sup>11</sup> states, "Psychodynamics is the name for the theory which brings order into psychoanalytic observation and into the material of data ascertained by such observation. Psychodynamics represents the organized body of psychoanalytic findings, complemented by results obtained through other methods of research. Because of its singular value for the understanding of human behavior, psychodynamics must take its place in medicine as a basic science."

If possible, the foregoing definitions should be consciously incorporated into our clinical attitudes. The physiologist speaks of psychomotor reactions. Should we not, then, consider these psychodynamic factors as giving rise to psychomotive forces? I wonder if the term psychomotive force does not have some justification! There is an analogy with the term electromotive force. Electromotive forces may be engendered by various qualitatively different phenomena. Thus, if two dissimilar metals are placed in a dilute acid an electromotive force arises. Similarly, changes of free surface energy or changes in the physical state of the

surfaces, induced by the rubbing or the stretching of rubber, may give rise to electrical potentials. Can we not consider that various integrated neurobiochemical mechanisms, such as frustration, anxiety, guilt, hostility, et cetera, may give rise to psychomotive forces, the clinical effects of which will become more clearly delineated as the accumulating data are classified systematically?

It is recognized that Freud used the expressions motive force and motive power. However, a motive force is merely one which gives motion. It is not sufficiently specifically defined. It is necessary to designate the motive forces under discussion as those derived from the psyche, that is, specifically *psychomotive* forces. We must, therefore, also recognize the existence of *neuromotive* forces like those, to take a simple example, engendered by the antidromal impulses which produce a flare in the skin surrounding the histamine or allergic wheal.

With these definitions in mind, a fraction of my case histories, which proved to me that the conscious use of psychodynamics will be of value to the allergist, will be briefly touched upon.

#### CASE RECORDS ON PATIENTS IN WHOM THE DIAGNOSIS OF ALLERGY IS DEFINITE

*Case 1.*—C. was an unmarried man of forty years who was receiving perennial pollen therapy. Upon giving him his usual dose on one occasion and using the same extract, he got a very severe local reaction. I was unable to explain this reaction when he stated, "I am under unusually intense emotional strain at present. Do you think that this could have influenced the reaction? I believe so!" Whether emotional stress will increase the severity of local and general reactions to pollen allergens during treatment, I should like to leave to the Panel for discussion.

*Case 2.*—J. B., a theological student, stated, "When I have hay fever during September, something quite interesting occurs. I may have hay fever prior to preaching, but the hay fever disappears when I reach the pulpit."

*Case 3.*—A similar sequence occurred in an actress, K., who was sensitive to pollens and dust. K. stated that while she very frequently, during the season, had very severe hay fever in the wings of the stage, the hay fever disappeared when she faced the audience.

One may speculate in various ways on the mechanisms leading to the sudden diminution of the symptoms of hay fever in these apparently simple situations. It is, however, of still greater interest to take up in more detail the next case.

*Case 4.*—J. S., an unmarried man, twenty-five years old, was first seen in 1935. At that time he was extremely clinically sensitive to pollens and other inhalants. He also was skin sensitive to many foods. Trained as an engineer, he found it difficult at that time to obtain professional employment because of the business depression. He was extremely radical in his political views and did not take kindly to our form of government.

He responded poorly to specific therapy by injections of pollens and dust and by elimination diets. However, he himself developed a technique of controlling his asthma by a very interesting and surprising procedure. He stated, "When I feel an attack of asthma coming on, I get furious with myself for having the asthma, and this seems to avert the attack."

According to the results of certain studies on the psychogenic factors in asthma, it appears that the suppression of hostility may lead to intensification of asthma. In this patient there is evidence that some similar mechanism may have intensified his symptoms. The patient was advised to reconsider his hostile attitude toward our present social system and, if possible, to fit in with it. After several interviews he decided to become a government employee. He was sent to Albany, N. Y., by the government, where because of his skill he was rapidly promoted. He shortly thereafter made a satisfactory marriage, with a very definite change in attitude toward his whole life situation, modifying in addition his political views. His letters indicated that he was practically free of asthma but that he had mild residual hay fever which was readily controlled by pollen therapy.

*Case 5.*—Another instance in which repressed hostility led to a serious asthma attack was in Mrs. Q. From 1936 to 1940, when she was unmarried, she had received pollen and dust therapy with satisfactory results. However, subsequent to her marriage there occurred serious asthmatic attacks, which at first were ascribed to food sensitivity. On Friday nights she visited her mother-in-law. At these dinners the patient usually partook of fish in various forms. And since skin reactivity to fish was moderately positive, there did not seem to be much doubt that her asthma was induced by injudicious ingestion of what to her was an allergenic food. Unfortunately, the problem was not solved that simply. A serious asthmatic attack started one Saturday morning at 2:00 a.m. and persisted for four days unabated. The patient at that time was in her fourth month of pregnancy. After prolonged discussion, in which the patient's relationship with various members of the family who were present for dinner the preceding Friday evening was discussed, the patient became very upset and started to stammer in describing a conversation with her sister-in-law. It seems that her sister-in-law had remarked that the patient's abdomen was too large for a pregnancy in the fourth month. The violence of the attitude of the patient toward her sister-in-law, as well as the stammering, indicated that the relationship with the sister-in-law was strained. This expression of hostility to her sister-in-law coincided with the very rapid disappearance of her severe asthmatic condition. Except for the usual occasional mild wheezing spells readily controlled by inhalation of epinephrine hydrochloride, a quiet period of several months followed, during which her Friday evening asthma ceased.

This patient's skin reactions fit quite clearly and classically into the immunologic model. The patient had already been married for some time, and there was no reason to believe that premarital relations had caused the pregnancy. The hostility toward the sister-in-law and the violence of her response to the remark that her abdomen was large must be based upon other experience or fantasy. It was apparently these unknown experiences or fantasies, unknown both to the patient and the doctor, superimposed on the immunologic pattern, which led to the aggravation of asthma.

*Case 6.*—This patient, a married woman, thirty-two years old, had two children and appeared happily married. However, one year before she was



first seen by me, mild asthmatic attacks which had previously been easily controlled became so severe that the patient became incapacitated and could no longer take care of her family duties. She had had asthmatic attacks of a mild nature during the preceding ten years, particularly associated with upper respiratory infection. There was no history of seasonal hay fever nor clinical intolerance to other allergens. The patient had travelled a considerable distance to see me and arrived in New York City in a somewhat anxious state. In her first interview she revealed that during the preceding year no one had really been able to help her and that I was a last resort. At that time my attention was focused on experimental work with mists, which resulted in the stabilization of the particle size of the 1:100 solution of epinephrine hydrochloride. This new epinephrine mixture was prescribed. Much to my regret, the nebulizer and the solution which I had highly recommended were ineffective. I then advised her to take a teaspoonful of a mixture containing 5 grains of chloral hydrate three to four times a day and to discontinue the epinephrine injections and ephedrine capsules upon which she had previously depended. After this recommendation she came to see me the next day, sat down, pulled the bottle of chloral hydrate out of her bag, took a drink from the bottle and said, "You struck oil."

In spite of such optimism, the patient phoned several days later that her asthma was more severe than ever. I saw the patient within one hour of hospitalization. She received me sitting up in bed and breathing with difficulty. However, on examination of the chest, no râles were heard and the breath sounds were exaggerated. These findings were confirmed by a consultant. The patient's difficulty was evidently both respiratory and asthmatic.

After several hours, the patient developed a severe status asthmaticus. If there had been more delay in the chest examination, the respiratory difficulty without asthma would not have been observed. Subsequent conversation with the patient led to the disclosure that there was a very unhappy and difficult marital situation, details of which need not concern us at this time. In addition to the usual symptomatic therapy of her asthma, psychoanalysis was advised, and later was undertaken by the patient.

*Case 7.*—C., a twenty-four-year-old, serious minded, unmarried woman, lived with parents who had set up rather high standards for her. An ailing father, who was unable to work, made it necessary for her to continue working in order to contribute to the family support. Clinically sensitive to pollen, dust and a variety of foods, she was unequivocally classified as an allergic individual. At times she had difficulty in controlling her seasonal asthma as well as the asthma attacks which occurred between seasons. Very often she lost her usual response to ephedrine and epinephrine. For this reason it was necessary to explore at length, but nevertheless superficially, her life situation. This was not successful.

I finally decided that I would try to control her asthma by teaching her a form of breathing exercise, in itself a very definite type of psychotherapy. In it, the patient is instructed to extend the hands forward while inhaling; on exhalation the hands are brought to the side, but during expiration the expiratory breath is made very slowly and a humming, crying sound is made through the closed lips. It is very interesting to see the reaction of patients when the exercise is demonstrated. The crying sound, of course, has many implications, and nine patients out of ten smile in a queer and embarrassed sort of way. However, the patient took readily to this type of exercise and reported her ability to avert

attacks by doing the breathing exercises when she felt an attack coming on. Patients are advised to perform this exercise from one to two minutes every hour on the hour during a period of tension and difficulty in controlling the wheezing in the chest. This patient improved considerably on utilizing this breathing exercise. As a matter of fact, she was able to use this exercise in the subways when she felt heaviness in the chest, by thinking of the movements and of the crying expiratory whimper which she had been instructed to carry out.

One of the most interesting groups of allergic individuals that may be encountered is the group with bronchial asthma, with the respiratory pattern not typical of asthma. In typical asthma, as we know, there is difficulty in expiration. However, it is always wise to ascertain if there is not a superimposed difficulty in inspiration. When there is inspiratory as well as expiratory difficulty, I have found it practical not to rely entirely upon epinephrine, either by inhalation or by injection.

In cases where the inspiratory difficulty appears to be greater, sedation may be more important in controlling the attack.

In certain instances epinephrine may not work at all and these patients are often considered to be "adrenalin fast." However, these people are far from "adrenalin fast" in a pharmacologic sense for they may not have been taking epinephrine for months. An acute asthmatic paroxysm may occur which does not respond at all to epinephrine, irrespective of the amount given. I have one patient who received 6 cubic centimeters of epinephrine, 1:1,000 solution, subcutaneously, during the course of one night without relief, but who responded quickly to moderate sedation. Another case in point is one that I have observed recently.

*Case 8.*—This patient was a married woman of thirty years of age who had moderately severe asthma for one week which did not respond to epinephrine or ephedrine. She was hospitalized, and 3 grains of sodium amytal were administered after meals, three times a day, with 1.5 grains of seconal and 10 grains of chloral hydrate before retiring. In spite of this profound sedation, with a minimum amount of epinephrine given by inhalation, this patient was alert, active and became asthma-free. During this time, in spite of the high degree of sedation, she showed none of the ordinary sedative effects except the beneficial effect on her respiratory difficulty. As a matter of fact, this patient has periods free of asthma at home, followed by periods of severe asthma which is essentially uncontrolled by epinephrine but definitely controlled by sedation. Now this patient is really allergic, with positive skin tests, and she gets asthma when exposed to various inhalants including cat and horse dander. However, under exceptionally controlled conditions in which the allergic factor remained relatively constant, the severe degree of her asthma, I feel, was dependent to a great extent upon her emotional status. The complete picture of this case illustrates a good example in which the complex psychodynamic factor must be controlled much more than the allergic component.

*Case 9.* A schoolgirl of thirteen years of age had long-standing allergic rhinitis, stuffed nose and sore throat. This began at the age of five when

she had begun coughing and had had frequent sore throats for which her tonsils and adenoids were removed. Since that time, she had had coughs and stuffed nose which were worse in September and October, suggesting ragweed sensitization. However, she also had had a stuffed nose very frequently in winter. At eleven, she became quite conscious of that fact. Her worse attacks, however, took place when the weather was consistently hot. This also fitted in with a diagnosis of constitutional hypersensitiveness. Her parents had paid considerable attention to keeping her in an allergen-free room with the usual precautions taken for mattress, pillow, rugs, curtains, et cetera. The patient had been told that she was constitutionally hypersensitive by her physician and had been given ragweed injections to no avail.

Physical examination of the patient was negative. There was a 7 per cent eosinophilia in the blood smear, confirming the diagnosis of allergy. There was no nasal discharge. Study of the skin reactivity revealed only suspicious reactions to a few foods. Reactions to ragweed pollen were slight with solutions containing 0.2 mg. N per c.c. Confirming the probability of ragweed sensitization was the presence of a moderate reaction to various tobacco extracts.

The clinical course of the patient, however, did not justify classifying this child as a simple case of hay fever. Late in May, during the grass season, she complained of a sore throat and clogged nose. On careful questioning, the sore throat turned out to be a lump in the throat, the patient herself stating that it was the "same that you get when you are about to cry." One week later, she visited her grandmother in a town nearby. As soon as she arrived at her grandmother's house, her nose became stuffed. This occurred fifteen minutes after she went inside the house, but cleared up while remaining within the house and was completely gone when she went to bed that evening. The following day, apparently helped by our discussion of the week before, instead of complaining to her mother of a sore throat, she told her mother that she had a lump in the throat. Her nose was not clogged and there was no cough. The lump in the throat this time lasted two or three hours and was relieved by steam inhalation. Again she explicitly stated to me that "my throat does not feel sore. Only feels as if something were caught there." After a few brief conversations the child was taught to distinguish between her emotional upsets on seeing her grandmother because she told her mother that "when I'm with Grandma I want no one there. Not even you—only Grandma." Further discussion led to the fact that she was anticipating the death of the grandmother. It was this idea which apparently had led to many of her symptoms.

She did not receive injections for her ragweed sensitization. Dust injections were given by her own physician. Her hay fever that year was so slight as to indicate that her pollen sensitization was a minor factor. The clinical course of the patient has been excellent without specific hypersensitization except for dust.

#### ALLERGIC PATTERNS IN INDIVIDUALS NOT PROVEN TO BE IMMUNOLOGICALLY ALLERGIC

In practically all of the cases with bilateral, wheezing respiratory difficulties (excluding tumors, stenoses, et cetera) which I have seen, there was some plausible type of immunologic, allergic or infectious basis. However, in the dermatoses, not in-

frequently there occur clinical entities similar to allergic responses where a true immunologic reaction cannot be unequivocally demonstrated. For example, a young married woman who was seen in 1940 complained of hives following ingestion of aspirin. Investigation revealed that she could take aspirin with no hives developing while under observation in my office, but on taking aspirin at home she invariably got hives. She had never had hives before her marriage. After her marriage she had almost always taken aspirin after quarreling with her husband. It ultimately became clear that it was not the aspirin but life situations of this type which led to hives.

In a study of several persons with hypersensitiveness (whealing response) to cold who were not immunologically allergic, a conflict situation was found in one case in an incident when the patient nearly drowned while swimming in the summer of 1941. A study revealed that these hives were apparently engendered by an unconscious death wish, the conscious realization of which led to a fairly rapid recovery. This case is of special interest and is given here in some detail.

*Case 10.*—A married woman, thirty-one years old, whose illness began on July 20, 1940, when she went swimming. On coming out of the water and drying herself as usual on the float in the sun, she discovered that she was "pink and itchy." This had never occurred before. She went into the water to cool off, but on coming out found that she was covered with small welts on the arms, legs and chest. Giant hives then formed all over the legs and arms, especially on the inside of the thighs. During the remainder of the time (eight weeks) which was spent near Long Island Sound, hives always formed on swimming if the immersion period was at all appreciable. The patient also noticed that on washing with cool or cold water, scattered hives also formed. This had never occurred prior to the first attack.

The patient had omitted the following fact in relating her history: she had almost drowned while in swimming the day before the onset, i.e., July 19, 1940.

Skin tests with a routine group of inhalants and foods were negative, and there was no history of food or other allergies, indicating that the patient belonged to the group having an allergic response without a true immunologic reaction.

There was no dermatographia nor was there any electrical urticaria. To definitely classify the case as one of a whealing response to cold, the patient was tested with a standard cold stimulus. Well formed wheals, pseudopods, developed after as short a period as one minute of application of this standard stimulus. The maximum height of the wheal after one minute of application of the stimulus was approximately 1 mm. Much larger wheals with marked spreading without formation of pseudopods occurred after five minutes of application. The fact that cold had not previously caused whealing raised this question. Why had the onset of this response occurred at this particular time, that is, on a certain day after swimming?

During the summer of 1940, incidental to the war in Europe, she was

upset considerably. In the summer preceding the outbreak of the war, I saw the patient frequently. In 1939 she was gay and vivacious and more or less enjoyed life; in 1940 there was a definite tendency to be upset by war reports. Three friends for whom she had had a special esteem were actively engaged in the British and French navies, two in the submarine service and one on the French battleship, *Bretagne*, which had been sunk before the patient's present illness. Although the reports of the sinking of two submarines, each with one of her friends, occurred subsequent to the whealing response to cold, the death of one friend on the *Bretagne* at Oran occurred shortly before the abnormal response to cold was manifested.

The patient stated that she was a hypersensitive type because she fainted easily. She did not like the idea of skin tests. On further questioning she retracted the statement that she fainted easily and said that she did not really faint easily but "a sudden shock will cause prolonged periods of crying." She had, however, fainted before the onset of the present illness. The patient herself emphasized that anything sudden might produce an emotional upset: "If someone is suddenly rude to me, I am finished. If I tumble down the stairs, I might not be hurt but would cry."

After discussing the onset of the symptoms, the patient stated that a good many incidents relative to the development of the syndrome described did not become clarified until after a particular interview six weeks later. One evening thereafter, she *volunteered* the following information. She stated that while swimming toward shore on July 19, previous to the occurrence of the hives (the day when she nearly drowned), she had really felt that she wanted to drown. She stated that she felt that she didn't deserve to live while her friends serving in the armed forces, younger than she, possibly more useful to humanity than she, had to die while she remained alive. She was quite certain that this conflict existed during the two times that she "went down."

The striking feature is the suddenness of the onset following a period of mental conflict which endangered the patient's life. Since an immunologic mechanism always involves the presence of a complete or partial antigen, and since there is no type of conventional allergic sensitization discovered in the case in question other than what one could call the presence of a sensitized state psychologically, it is not apparent how one may think of the whealing response to cold described here as similar to the ordinary allergies. Rather, one must look here for a psychological pattern which can change the physiological processes in the system, as in this case, suddenly, in such a way that there is both a qualitative and quantitative change in the response of the minute vessels of the skin to the stimulus of cold. Although it may be argued that some immunologic reactions of the patient might have been altered, it is not likely that any known immunologic mechanism is primarily involved in the whealing response to cold itself in this case.

On one occasion when the patient had remained in the water about ten minutes, there occurred a severe skin reaction. In spite of the severity of this reaction, only slight dizziness was experienced. The main symptom was generalized itchiness, without anxiety, fainting feeling, or feeling of impending collapse. In other words, there was no general histamine-like reaction.

The patient moved to a cold climate after the acknowledgment of the conflict. She wrote (January 30, 1941), "Apparently you are quite right about my allergy—for the calmer I become about my friend's death the

slighter the trouble. I can put hand or foot in cold water now with no swelling, but if I go out in a cold wind, I return looking as though I had been having a bout with Joe Louis. However, it returns more or less to normal within an hour."

About one year after the onset of her illness, she returned for examination and reported the following details about the loss of her whealing response to cold. She stated that at first she was not convinced that the origin of her urticaria was psychological. However, she developed "a new point of view," made new friends, and gained 10 pounds in weight. Thereafter, she noticed that she did not wheal as usual. In the summer of 1941 the patient was taken to the same spot in which the conflict discussed in the foregoing was described. She swam to the same boat and back to the same pier. There was no evidence of any urticarial response whatsoever.

*Case 11.*—In the following case, the allergen was accidentally suggested to the patient. B. was a pretty girl of nineteen, well dressed for a clinic patient, with better manners than usual and better education than one ordinarily encounters in the clinic in question. She complained of hives of six months' duration. This patient's skin tests were negative. However, elimination diets were of no avail. About ten days before Christmas in 1941, various allergic possibilities causing hives were discussed with the patient. The role of inhalants was mentioned, and I accidentally said that perhaps even the odor of Christmas trees which were then being offered for sale could produce hives in certain individuals. The patient apparently seized upon the suggestion that the odor of Christmas trees was causing her hives. The following week, she came back full of confidence, for she was able to produce hives on going close to a large number of Christmas trees then being sold. During the following month (January, 1942) the hives persisted even though she was no longer exposed to Christmas trees. This was pointed out to her. She was asked if she could make sense out of the whole thing. She then requested to speak to me privately. We went to another room where no one could overhear our conversation. She wept bitterly. Her parents had separated when she was quite young. The burden of her education and upbringing fell upon her mother. She felt that she was not receiving all of the education and its advantages which she desired and required. The patient was placed on a full diet. In a period of months her attacks of hives were replaced by milder and less frequent episodes.

It may be argued in this case that our immunologic model in my hands did not serve satisfactorily. Be that as it may, it was quite evident from the course of the case that the suggestion that the odor of Christmas trees produced hives was followed by the production of hives. This case is presented to show that a pattern classically allergic may also be produced by conditions in which the immunologic model as yet is not clear cut, if, indeed, it is present at all.

*Case 12.*—An unmarried lawyer, A. B., thirty-eight years old, complained of asthma, eczema and hay fever. His symptoms had been present periodically for about six months.

Each one of these complaints merits separate attention. At no time while the patient was under observation was any asthma noted, nor could he justify his history of asthma by a description of a true asthmatic attack. There was present some difficulty in breathing or some modification

of the respiratory cycle at times. This respiratory difficulty was misinterpreted by the patient and his friends.

The eczema was localized to the scalp and was diagnosed as mild-seborrheic dermatitis which readily responded to appropriate treatment.

The complaint of hay fever seemed to be justified and was essentially the main symptom. It was not induced by temperature changes, nor was it exaggerated by dust, perfumes, foods or any of the allergens responsible for rhinitis. The family and past personal history for allergy was negative.

The patient was well developed, well nourished, co-operative, far above the average intelligence, and a meticulous person in dress and in manners. Rapport was readily established when the usual medical matters were discussed. It was evident, however, that the usual routine physical and laboratory examinations were not only important from the point of view of the physician but also from that of the patient, who showed more than a casual interest in their outcome. Physical examination, as well as laboratory findings, were negative, including the skin reactivity to an extensive series of allergens, including dusts from various sources, pollens, foods and mold spores. There was no local condition in the nose to account for the symptoms nor was there any eosinophilia in the blood.

A more detailed analysis of the time of occurrence of the hay fever was undertaken. The patient finally revealed that his hay fever occurred chiefly after fatigue or nervous strain. He volunteered that if he stayed up late at night he had severe hay fever the next day. In spite of the fact that the patient recognized the relationship of these nasal symptoms to his emotional state, this recognition did not result in any diminution of symptoms. The patient challenged me to do something about his symptoms. The usual local medicinal therapy was employed to no avail. On a basis of empiricism, injections of dust and stock "cold" vaccine were suggested but were rejected by the patient.

The patient was discharged without relief and went to another city. Four months later, the patient reappeared and announced that his hay fever had practically disappeared but that he was feeling very depressed and was extremely unhappy. After some discussion he made the following disclosure: During the time that the allergic status of the patient had been investigated, he had been interested in a young woman whom he had seriously considered marrying. During his absence she had married someone else. It was this fact which occasioned his feeling of depression, coincident, however, with the disappearance of his "hay fever." He emphasized that he had really always been very uncertain in his attitude toward the young woman in question. He was extremely perturbed because he felt that he had not done the right thing by not marrying her. During subsequent conversations which touched on personal relationships and obligations, he appeared to be much relieved and much more cheerful. He then made a special appointment when he appeared with a new friend, feminine, blonde, and attractive, and without much ado he introduced the young woman and then said goodbye.

*Case 13*—The effect of a suppressed conflict on the origin of "allergy" to light has to my knowledge not been shown hitherto.<sup>1</sup> A patient who responds to irradiation by ultraviolet light by whealing of the skin has been studied, both from a physiological and psychological point of view. Although these studies are not complete, it is desirable to report progress made thus far. The patient is a married woman, W.G.H., forty years of age, whose skin shows a general response of hypersensitiveness to ultra-

violet light by a whealing reaction over all the body surfaces studied. The wave length at which whealing may be produced begins very close to 3,700 Å and extends to lower wave lengths with increasing sensitiveness in the region where absorption by the outer epidermis occurs. The patient

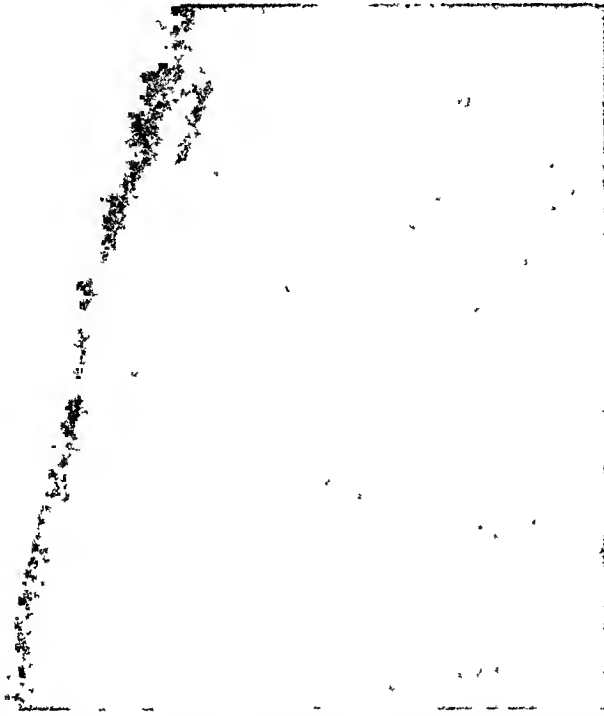


Fig. 1. Compare the sharp edge of the typical whealing response to light with the irregular edge of the wheal produced by histamine (electrophoresis). This is evidence that the light reaction is not caused by a small molecule like histamine.

was referred by another physician who had explored therapy from the point of view of many of the theories dealing with the whealing response, including a high calcium diet, vitamins, as well as irradiation of the blood serum itself, followed by re-injections. The patient was subjected to many types of conventional therapy without any success. The *original* history of the patient was as follows:

Approximately eight years before the patient came under observation, she went swimming at a nearby beach. She remained on the beach several hours. Following this exposure to sunshine on the beach, she suffered an attack of "sun stroke" and remained in bed, ill, for two weeks. When she recovered from her attack of "sun stroke," she noticed that she swelled up whenever she went out into the sunshine, especially in the summer sunshine. She could expose herself to sunshine in the winter to a certain extent. Protection by window glass was incomplete. The severity of her skin reaction was so great that she was unable to perform her ordinary duties as a housewife. In the summer, it was almost impossible for her to go out into the street because, even though she carried a parasol, reflected ultraviolet rays caused very severe edema of the ankles and legs.



Similarly, even when driving in a motor car, the reaction to reflected ultra-violet was quite severe unless the windows were closed.

After being under observation and submitting to many tests for a period of three years, a state of anxiety supervened. She related her symptoms

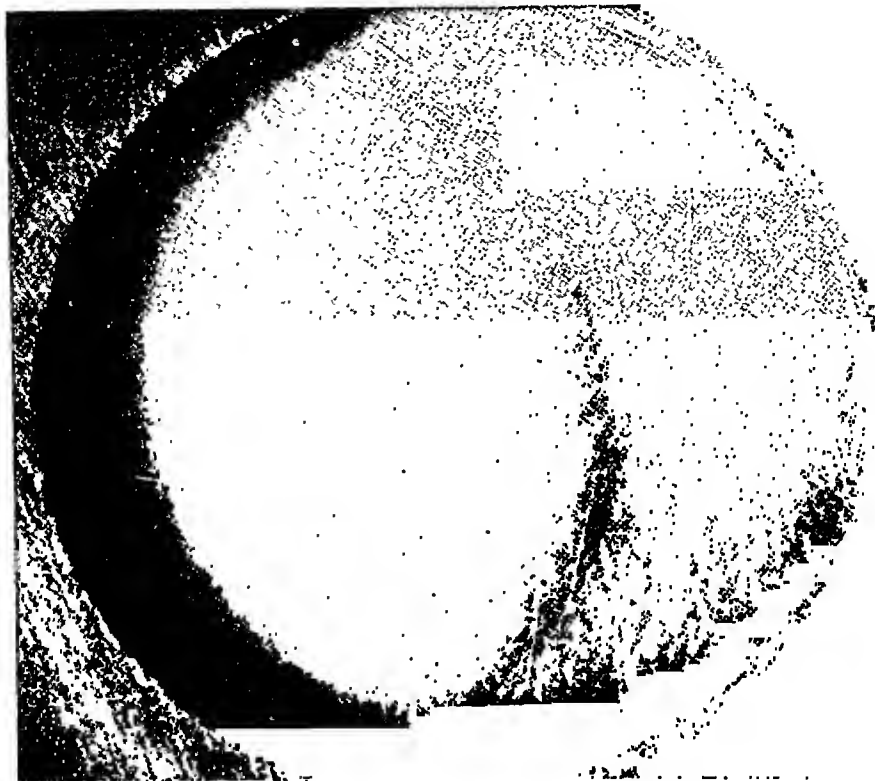


Fig. 2. Whealing response to cold produced by a standard stimulus. Note the absence of pseudopods. Magnification X 3.

to "early change of life," and endocrine therapy was instituted. At the same time, her history was cautiously re-explored, especially concerning the exact time when the whealing response to light first occurred. After many interviews, the following additional aspects in the history became clearer.

The patient and her sister were orphans and had lived together as unmarried girls. Subsequent to the marriage of the sister, the patient resided with her sister and husband. During the time that she lived with her sister, the sister's husband made advances which were rejected by the patient. Because of this difficult situation, she was forced to leave her sister's household without an adequate explanation. This gave rise to a complex family situation.

On careful questioning, it appeared that on the day the patient was in swimming (the day subsequent to which she developed *urticaria solare*) the sister and her husband unexpectedly appeared at the beach. On seeing her sister and her brother-in-law, the patient ran into the water and remained partially submerged in the water for three hours, explaining to me: "I did not want him to see me in my bathing suit." It was only after her sister and brother-in-law had left the beach, that she came out of the water and subsequently became ill.

After tracing the events of the intervening years, during which she had married and there had been no amelioration of the difficult family situation, the patient's present and newly precipitated state of acute anxiety seemed to have been occasioned by an unexpected visit of her brother-in-law when she was at home alone. This unexpected visit had preceded her new symptoms.

Further questioning only led to a repetition of the above story. The seriousness of the emotional reaction of the patient led to further exploration. It appeared that something in our folklore would lead to an explanation. It was customary in Biblical times for a husband, on the death of his wife, to marry the sister of the wife. This was cautiously explained to the patient and she was asked if any situation corresponding to that ever arose. Her answer was immediate. She said, "Of course. He always told me, 'When your sister dies, I'm going to marry you.'" No attempt has been made as yet to explore this lead, although the conflict situation produced anxieties and organ neuroses readily "cured" by placebos. Her sensitivity to light has persisted unchanged.

The most common cause of the skin wheal, dermographism has no immunologic basis whatsoever.

#### EMOTIONAL DISTURBANCES—CAUSE OR EFFECT?

The relationship of the emotional disturbance to the development of the allergic pattern may be considered from two points of view. In the first place, the emotional disturbance may play a role in choosing the organ and changing the neurovascular system so that the thresholds are lowered and the intensity of the allergic pattern is increased or decreased. In the second place, the resultant allergic syndrome may have a special effect itself on the emotions of the individual so that a vicious cycle arises. This question has been considered by Rogerson, Hardcastle and Duguid,<sup>12</sup> who asked whether the intense need of children with bronchial asthma for mother's love is one of the causes of their asthmatic condition or a result of it. There was much to suggest that the acute dependence on the love of the mother might result from the asthmatic attacks themselves. If I may quote French:<sup>5</sup> "A severe attack of asthma, with its acute threat of suffocation, is a terrifying experience and one in which the patient feels completely helpless. What wonder, then, that a child who is constantly threatened with the danger of suffocation and whose activity must be limited for fear of bringing on an attack should feel the need always to have near him a mother to whom he can cling? There is, accordingly, every reason to expect that the asthma attacks themselves should induce just the sort of helpless dependence that has been found to be characteristic of the deeper emotional life of our asthma patients. May not the personality traits that we have been describing be merely a secondary reaction to the disease itself?"

There are, of course, too few data to draw any unequivocal conclusions. I hope that the members of the Panel and of the College will discuss, for the record, in what way they believe

that the allergic patterns, especially asthma and skin manifestations in the infant, in the child and during later life, may influence the personality structure.

#### THE COMBAT EQUIVALENT IN THE ALLERGIC PATIENT

It was shown by Peshkin<sup>8,9</sup> in 1922 that in a group of 500 children considered otherwise relatively normal (no clinical allergy), approximately 10 per cent showed positive skin tests to a variety of allergens. He observed these children during a period of years. He found that some of these immunologically positive children were often precipitated into acute episodes of clinical allergy, especially asthma, by other presumably unrelated conditions, as for example, whooping cough, measles, pneumonia, upper respiratory infections, and even following operations for the removal of tonsils and adenoids. It is of interest that Peshkin regarded these superimposed diseases or procedures as the initiating factors which led to the clinical manifestations which had been viewed in a preliminary way by the immunologic reactions in the skin. In 1926, Peshkin further developed his concepts to the point where he proposed the clinical syndrome of para-asthma. The term para-asthma was introduced to segregate bronchial asthma due to immunologic hypersensitiveness from asthma not due to immunologic hypersensitiveness. Similarly the term para-allergy may be utilized. Since infection or trauma could influence the onset of allergic patterns in individuals previously shown to be allergic without clinical patterns, why cannot disturbances neurogenic in essence produce similar reactions, perhaps even to initiate them? These could be included in the para-allergy group. All of this implies that the immunologically allergic individual already has patterns carved as it were by his response to allergens. In the individual without known immunologic patterns, these patterns nevertheless exist, as we know from clinical experience. These patterns exist just below an explosive threshold where another stimulus, such as a difficult life situation, may result in an overwhelming clinical response. These life situations can possibly be considered analogous to combat equivalents. The argument may be raised that combat situations are not similar to ordinary life situations. That view is open to question. The combat situation really occurred the first day war was declared or war was imminent. It might have expressed itself clinically upon notification by the draft board to report or in more rugged individuals only after prolonged periods of combat. If one accepts the point of view that many of these individuals who have been subjected to difficult combat situations were subsequently successfully treated by physicians rapidly trained in psychodynamics, we might have another basis for rapprochement between allergy and psycho-

dynamics. This possibility will be touched upon briefly in the next section. In it we will assume that the allergic individual faces, in his daily routine, life situations which may be combat equivalents. The immunologic model and the clinical pattern has already been deeply carved into his physiologic structure so that given certain types of life situations the clinical response is very much out of proportion to the situation itself.

#### FUTURE PROGRESS

There are two steps necessary to achieve a fundamental advance in the specialty of allergy as far as its relationship to psychodynamics is concerned. The first step involves a change in the editorial policy of the leading journals devoted to allergy and to psychosomatic medicine itself. It would, for example, be refreshing to find case records in the journal, *Psychosomatic Medicine*, showing that a pattern typically psychogenic in nature turned out to be based upon an immunologic mechanism. Similarly, contributions designed to emphasize the role of emotional factors in the allergic patient must be encouraged, even sought, by the editorial staffs of the allergy journals.

The second step involves systematic postgraduate instruction in psychodynamics. Ideally, a personal psychoanalysis should be a requirement for the study of psychodynamics. But at present this preparation must, in general, be reserved for the student and the younger physician. Few of this younger group will become psychoanalytically trained allergists under our present system of training and specialization. Cannot this problem be answered by comparable situations of the last war? The acute war neuroses were often successfully treated by physicians rapidly trained in psychodynamics. If the great mass of data which now comprises the basic science of psychodynamics were to be classified into a form capable of being more easily understood and applied by the allergist, an important advance in the science and practice of allergy itself would take place. Allergy would then become a more useful specialty than that which could be provided by either the allergist or by the psychiatrist working alone.

Some may conclude, in view of our present knowledge and attitudes that these steps are either undesirable or impossible to attain. However, an appreciable number of my colleagues and I believe that with proper instruction and proper sympathy, this program is neither impossible nor undesirable. The success of this proposed publication and instructional program cannot be estimated until a serious attempt is made to carry it out under suitable auspices. Without such an attempt, neither group will be able to understand the other or help the other group to synthe-

size the complicated psychosomatic syndromes under discussion, during our time. With this attempt, perhaps implemented and encouraged by this Round Table, a new and broader phase of clinical allergy will have been initiated.

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# SKIN TESTS WITH ENDOCRINE SUBSTANCES

## Method of Zondek and Bromberg

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IN 1934, Sulzberger, Rostenberg and Sher<sup>10</sup> reported on skin tests with hormones in cutaneous diseases, notably acne vulgaris, and in the text book on *Dermatologic Allergy* Sulzberger<sup>8</sup> reviewed the experimental data on endocrine allergy and discussed at length the possibility that acne and other dermatoses might be related to the allergic hypersensitivity of cutaneous structures to autochthonous hormones. In addition, among others, Simon<sup>7,8</sup> and Loveless<sup>3</sup> have reported experiments demonstrating the existence of true allergy to hormones.

More recent and extensive studies were reported in 1945 by Zondek and Bromberg,<sup>12,13</sup> who obtained positive skin tests with a large variety of hormones and interpreted their results as indicating a state of allergic hypersensitivity to hormones produced by the endocrine glands of certain individuals. Among the various diseases in which they found some cases to be due to hypersensitivity to hormones, there were several of dermatologic interest. The present study, which was restricted to tests with steroid hormones, was undertaken to examine the diagnostic and therapeutic applicability of the method of Zondek and Bromberg in a larger dermatologic material.

Zondek and Bromberg observed the existence of a state of hypersensitivity both to protein-like hormones, e.g., insulin and pituitary secretions, and to steroid hormones (estradiol, progesterone, testosterone, and corticosterone). Hypersensitivity to the steroid hormones, or to the products of their metabolism which are excreted in the urine (estrone, pregnandiol, and androsterone), was demonstrated by cutaneous tests with oily solutions; such tests usually became positive within twenty-four to forty-eight hours. Hypersensitivity to insulin and chorionic gonadotropin was demonstrated by cutaneous tests with aqueous solutions; such tests usually became positive after a shorter reaction time.

The conditions included in their study<sup>9</sup> were cases of the following diseases in which certain pathological conditions became manifest in relation to menstruation or menopause: (1) asthma, (2) vasomotor rhinitis, (3) angioneurotic edema, (4) chronic urticaria, (5) chronic eczema, (6)

These studies were carried out under a fellowship grant for research in dermatologic allergy given by Luzier's, Inc., through the American College of Allergists.

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The authors are indebted to Dr. F. L. Mohr of the Ciba Pharmaceutical Company for supplying all the test solutions used in these studies.

acne, (7) migraine, (8) superficial keratitis, (9) premenstrual tension, (10) pruritus vulvae, and (11) premenstrual fever.

The following items are listed by Zondek and Bromberg<sup>12,13</sup> as evidences of endocrine allergy:

1. Positive skin tests demonstrating hypersensitivity to oily solutions of steroid hormones or to their products of metabolism.

2. The "recurrent test reaction," i.e., specific flare-up of the original cutaneous test site when a larger quantity of the same steroid hormone is injected subcutaneously twenty-four hours later at a second site. This reaction tends to show that the reaction to the particular hormone is specific.

3. The "retarded or periodic retarded reaction," i.e., the premenstrual flare-up of a specific test site occurring in the same phase of one or more successive menstrual cycles indicating sensitivity coincident with the peak concentration of the hormones in the body.

4. Serious reactions of an allergic nature following the injection of even minute amounts of steroid hormones in allergic patients not previously treated with hormones.

5. The ability to demonstrate the presence of specific reagins to a hormone by means of passive transfer tests.

6. The "endogenous passive transfer test," i.e., when during the premenstrual phase "normal" subjects were injected intracutaneously with serum from patients hypersensitive to estrone or estradiol, they gave positive cutaneous tests. This demonstrates that serum reagins can produce positive cutaneous reactions when the allergenic hormone reaches its peak value in the body of the "normal" patient.

7. Similarities in the properties of hormone reagins and ordinary reagins.

8. The fact that patients with a positive cutaneous reaction to a hormone often give a personal and family history of allergic disease.

9. The fact that hyposensitization with the allergenic hormone is often accomplished with satisfactory clinical results.

#### PREPARATION OF THE STEROID HORMONE TEST SOLUTIONS

As previously stated, we restricted ourselves to tests with steroid hormones. This was done because of the infrequent occurrence of positive reactions to pregnandiol, insulin and chorionic gonadotropin, as reported by Zondek and Bromberg. The materials used by us included the recrystallized steroid hormones estrone, estradiol, progesterone, testosterone, androsterone and de-oxy corticosterone acetate; in addition to these, cholesterol and the olive oil vehicle alone were used as control materials.

The steroid hormones and cholesterol were dissolved in neutralized olive

oil.\* This was accomplished by heating each of the mixtures at 100° centigrade for twenty-four hours, until a sterile, clear, and homogeneous solution was obtained. All substances were prepared in concentrations of 1 mg. of hormone in 1 c.c. of olive oil, and were dispensed in sterile rubber-capped vials.

#### METHODS OF TESTING

In the beginning we used the volar surface of both forearms, and all tests were made by the classical intradermal technique, as suggested in the original paper by Zondek and Bromberg.<sup>12</sup>

Fifty-six subjects were tested by this method. The almost regular appearance of local reactions which were equal to or greater than the positive reactions described by Zondek and Bromberg led us to question the correctness of our method of testing. It was evident that 0.1 c.c. of the olive oil vehicle, with or without the steroid hormones, when injected intradermally, acted to produce local non-specific reactions.

Subsequently, in a personal demonstration by Dr. Zondek, we were shown that the method which he and Bromberg had actually used<sup>13</sup> was to insert the needle through the epidermis to a level *somewhat deeper* than that usually used for intradermal testing. When the oily material was injected in this manner, a small elevation of the skin was produced which disappeared almost immediately. The injections were made into the lateral aspects of the arms and the radial aspect of the forearms as follows: in the right arm, the proximal site with cholesterol and the distal site with estradiol; in the right forearm, the proximal site with estrone and the distal site with progesterone; in the left arm the proximal site with the olive oil vehicle and the distal site with testosterone; and in the left forearm, the proximal site with androsterone and the distal site with desoxycorticosterone acetate. In order to be able to exactly locate the site of injection by this method at the time of reading each site was indicated by a skin marking pencil.

#### READING OF THE CUTANEOUS TESTS

The tested areas were observed twenty-four and forty-eight hours after injection. A reaction was considered positive (Table I) when, twenty-

\*Neutralized olive oil was prepared exactly as did Zondek and Bromberg, i.e., according to the *Helvetica Pharmacofoera* IV, as follows:

Olive oil	500.00 grams
Sodium carbonate dehydrate Rgt. q. s.	
Distilled water q. s.	
Sodium sulfate anhydrous	25.00 grams
Sodium chloride C. P.	12.50 grams

The acid value of the olive oil is first determined. This value multiplied by 0.6 gives the necessary quantity of crystalline sodium carbonate for 100 parts of oil. The sodium carbonate is dissolved in one half its weight of distilled water at 40° C. and added to the oil which has also been warmed to 40° C. Shake frequently and vigorously for 24 hours. The acid value is determined and if not sufficiently low, shaking must be continued until the correct value is reached. Then 5 parts of sodium sulfate anhydrous and 2.5 parts of sodium chloride are added to the oil and the flask is vigorously shaken. After 12 hours the mixture is filtered and the filtrate put into 100 c.c. flasks. These are stoppered and sterilized by heating at 115° C. for 15 minutes in an autoclave. Protect from light.

Assay.—Must meet the specifications of the olive oil monograph; however, the acidity must not be higher than 0.2 which corresponds to a maximum content of 0.0565 per cent of oleic acid in neutralized sterilized olive oil.



four or forty-eight hours after injection, a red or rose-colored slightly elevated area, at least 1.5 cm. to 3.0 cm. in diameter, appeared at the site of injection. Even when the twenty-four-hour reading was negative or inconclusive, a second reading was made at forty-eight hours.

TABLE I. EVALUATION OF REACTION TO CUTANEOUS INJECTIONS OF STEROID HORMONES

Reaction After		Evaluation
24 Hours	48 Hours	
+	+	Positive
—	+	Positive
+	—	Positive
—	—	Negative

The "recurrent test reaction" was used in those instances when doubtful reactions were observed in the regular test, e.g., in cases of positive reactions which appeared three to five hours after injection and disappeared a few hours later, or in cases of doubtful positive reactions at twenty-four to forty-eight hours. The routine of the "recurrent test reaction" is as follows: twenty-four hours after the cutaneous injection of 0.1 c.c. (0.1 mg.) of the test hormone, 1.0 c.c. (1.0 mg.) of the particular hormone which produced a doubtful reaction is injected *subcutaneously* at a site removed from the original test area. The test is considered positive if, three to five hours after the second (1.0 c.c.) injection, the original cutaneous test site evidences reddening accompanied by itching.

Our subjects were also observed for the "retarded reaction" and "periodic retarded reaction." For example, reactions which were negative at the twenty-four and forty-eight-hour readings but became positive just prior to the succeeding menstrual period were considered "retarded reactions"; and positive reactions which recurred spontaneously at the same test site during the premenstrual period of several successive cycles were considered "periodic retarded reactions."

We did not perform any passive transfer tests during this study.

#### SUBJECTS

The patients used for these tests were taken from among those at the clinic and in private practice.

A total of 102 patients was tested. There were sixteen men and eighty-six women. Thirty-eight of the eighty-six women presented dermatoses occurring with or apparently aggravated by menstruation or menopause. The remaining forty-eight women in whom the dermatosis presented no apparent relationship to endocrine function, together with the sixteen men, served as controls. As the work was done in the allergy department of the New York Skin and Cancer Unit, many of the "control" subjects presented eczematous, eczematoid and urticarial eruptions, including a substantial number of cases of a probable allergic etiology.

TABLE 11. PATIENTS WITH DERMATOSES APPARENTLY RELATED TO MENSTRUATION OR MENOPAUSE

Dermatosis	Number of Cases Tested	Number of Hormone Sensitive Cases	Hormonal Allergen	Effects of Hyposen-sitization Therapy	Number of Cases With Questionable Reactions of Any Type
Acne	12	1	Progesterone	Not done	2
Urticaria	7	2	Estradiol	Satisfactory	3
Pruritus vulvae	4		Estrone	Satisfactory	1
Eczema	3				1
Pruritus ani	1	1	Estradiol	Not done	
Generalized pruritus	1				1
Acne rosacea	1				1
Keratoderma climactericum	1				1
Keratosis follicularis	1				1
Recurrent aphthous ulcers	1				
Seborrheic dermatitis	1				

## RESULTS

*Subjects with Dermatoses Apparently Related to Endocrine Function*

Of the thirty-eight patients tested, having dermatoses apparently related to endocrine function, our skin tests indicated that five were apparently hypersensitive to the olive oil vehicle and therefore were excluded from further study. Of the remaining thirty-three patients, four presented their dermatosis as chronologically related to menopause, and twenty-nine as related to menstruation. The dermatoses studied (Table 11) were as follows: acne twelve, urticaria seven, pruritus vulvae four, eczema three, pruritus ani one, generalized pruritus one, acne rosacea one, keratoderma climactericum one, keratosis follicularis one, recurrent aphthous ulcers one, and seborrheic dermatitis one.

Four of these patients gave what were considered as positive reactions to the hormonal tests. Three of these gave positive reactions at the time of regular readings of the tests: one case of urticaria was positive to estrone; one case of urticaria was positive to estradiol; and one case of acne was positive to progesterone. The fourth patient, complaining of pruritus ani, was negative at the time of testing but gave a positive "retarded reaction" to estradiol prior to the succeeding menses.

Eleven patients gave questionable and inconclusive responses of various types. Six patients gave questionable reactions to one or more test substances at twenty-four hours alone or at both twenty-four and forty-eight hours. Four of these were tested a second time because of questionable reactions obtained with the first tests. The second tests did not give additional information. There were questionable "retarded reactions" in two patients. The "recurrent test" was done in three of the patients giving questionable reactions during the first tests, without obtaining a positive response in any case.

Unfortunately, two of the patients with positive reactions (the patients with acne and pruritus ani) could not be followed. The two patients with urticaria who gave positive reactions on cutaneous testing were hyposen-

sitized by repeated subcutaneous injections of ascending doses of the specific endocrine substance which had produced the positive skin test; both patients obtained marked relief from their disease.

*Case 1.*—A married woman, aged thirty-seven, mother of one child, complained of chronic urticaria with premenstrual exacerbations.†

The patient had recurrent attacks of urticaria since childhood, with rather severe attacks at the ages of ten and eighteen. In 1941, the patient noted that the attacks were becoming more severe and were occurring more frequently and that there was a marked flare-up of the urticaria during the premenstrual period. Therapy for a three-month period, consisting of stilbestrol and thyroid, produced some improvement of her condition.

During the next four years there were continued recurrent attacks of urticaria, for which numerous methods of treatment were tried, including calcium strontium bromide, ephedrine and Nembutal capsules, epinephrine, charcoal tablets, calcium gluconate, dilute hydrochloric acid, prostigmine drops, vitamin C, Hapamine, Benadryl, elimination diets and autohemotherapy; moderate temporary relief was affected by these methods. Hypnosis also was used and almost completely relieved the itching, but had no effect on the number or severity of the urticarial attacks.

In 1945, because of the definite premenstrual flares of the urticaria, which had been particularly troublesome for the eighteen months preceding, Dr. A. C. J. Simard instituted "autogenous" therapy with material prepared by Dr. Julius Pincus from the menstrual discharge of the patient, collected at the beginning of the flow; after dilution with saline and sterilization by Seitz filtration this was given in small subcutaneous doses every other day for a period of about five weeks. This treatment effected a complete subsidence of all urticaria.

The patient remained free of all urticaria until July, 1947, at which time a premenstrual flare-up of the urticaria was noted. Pyribenzamine aided in controlling the severity of the eruption. On August 12, 1947, the hormonal tests with endocrine substances were performed. At twenty-four hours the estrone site was positive (2 by 2 cm.) and at forty-eight hours the same site was still positive but the reaction was diminished in intensity. A "recurrent test" performed on August 14 was negative.

In view of (1) the history of premenstrual flare-ups of the patient's urticaria, (2) successful previous hyposensitization with autogenous menstrual discharge, and (3) a positive reaction to estrone on skin testing, hyposensitization with estrone was attempted. Daily subcutaneous injections of Thelin in oil (Parke, Davis), which is estrone in peanut oil, were given beginning with 0.1 c.c. In spite of maintaining the dose at 0.1 c.c. daily for a period of one week, the patient occasionally had exacerbations of her urticaria. It was impossible to ascertain whether or not the hormonal injections were the cause of these exacerbations. The dose was then gradually increased, and a total of thirty-two injections were given daily except Sundays. Thereafter, they were given three times weekly until a total of forty-three had been administered, the last five being 1.0 c.c. administered intramuscularly. Treatment was discontinued on October 24 because the patient complained of increased menstrual flow with an accompanying severe headache. Upon completion of therapy, the patient stated that she was "98 per cent" improved, with only an occasional urticarial lesion.

During the period of hyposensitization, the use of Pyribenzamine was not denied. Whereas the patient took up to 400 mg. a day at the beginning of treatment, the dose was decreased to none or 50 mg. a day at the end of treatment. It was interest-

†We are indebted to Dr. Charles R. Rein for referring this case.

ing to note that on several occasions the site of injection of the previous day flared when the succeeding injection was given ("recurrent test reaction?"). The flare-ups of the urticaria became progressively less toward the end of therapy.

The two subsequent menstrual periods (November 21 and December 18) were normal in character, with only a very slight increase in the number of urticarial lesions premenstrually.

On January 12, 1948, we retested the patient with cholesterol, estradiol, estrone, progesterone in olive oil and olive oil alone. With the exception of a very faint erythema and slight induration at the estrone site, all tests were negative at twenty-four and forty-eight hours. It appeared that the skin sensitivity to estrone had been greatly reduced as compared with the original reaction to skin testing.

*Case 2.*—A married woman, aged thirty-eight, mother of four children, complained of chronic urticaria with premenstrual exacerbations.

There was no history of atopy or previous skin disease, and she had a normal menstrual history. In June, 1943, two months following her last pregnancy, the patient was confined to bed for two months with "migratory rheumatism."

The patient recalled the onset of urticaria on her arms November 18, 1945. The date was associated with sudden cessation of her menses one hour after onset, which occurred on November 16, when she was severely frightened by an accident to her daughter. There was no menstrual bleeding until the following month when her regular period was preceded by dysmenorrhea, low backache, and marked generalized urticaria. Thereafter, the patient had mild urticarial lesions daily, with exacerbations starting ten days premenstrually and improvement with onset of menses. In March, 1946, the premenstrual period was further complicated by nausea and vomiting. Pyribenzamine helped to control the severity of the eruption after two weeks of hospitalization and the care of several physicians had failed to improve her condition.

The patient was first seen on September 12, 1946, at which time she presented a severe urticaria. Tests with endocrine substances were done according to the original intradermal technique (see above), and because of the nonspecific oil reactions the results could not be evaluated. On January 5, 1947, the tests were repeated by the same method, again with unsatisfactory results. The patient offered the information that several days following each of the tests she experienced a slight relief of her urticaria.

On January 20, 1946, the tests were performed with the correct, i.e., our definitive, technique. The twenty-four-hour reading was negative, but the forty-eight-hour reading revealed a questionable reaction to estrone.

On January 27 the tests were repeated on the thighs. The twenty-four-hour reading gave questionable reactions to estrone and progesterone; at the forty-eight-hour reading the previously questionable sites were negative and the estradiol site was positive (3 by 1 cm., erythematous and elevated, with itching). On the following day, January 30, the "recurrent test" was performed by injecting 1 c.c. of estradiol in olive oil subcutaneously. The area of the 1 c.c. subcutaneous injection rapidly became erythematous and edematous, and within one hour generalized urticaria appeared over the body. At the same time the estradiol test site on the right arm from the previous week flared (3 by 2 cm., erythematous and elevated). On the basis of these reactions, hyposensitization was undertaken with the same estradiol solution as used for skin testing.

Treatment was started on February 17, 1947, 0.1 c.c. doses being administered subcutaneously three times weekly for three weeks, with slight improvement of the urticaria. The dose was raised to 0.2 c.c. for another week with continued slight progress. When 0.3 c.c. was administered, the patient suffered her worst flare-up since starting treatment. Two additional attempts to increase the dose from 0.2 to 0.3

# SKIN TESTS WITH ENDOCRINE SUBSTANCES—BAER ET AL

TABLE III. CONTROL CASES—PATIENTS WITH DERMATOSES NOT RELATED TO MENSTRUATION OR MENOPAUSE

Dermatosis	Number of Cases Tested	Number of Hormone Sensitive Cases	Hormonal Allergen	Effects of Hyposensitization Therapy	Number of Cases With Questionable Reactions of Any Type
Eczema	23				6
Aene	20				1
Urticaria	7				2
Pruritus vulvae	3				1
Atopic dermatitis	2				
Chronic lichenoid and discoid exudative dermatosis	1				
Pruritus ani	1				
Granuloma annulare	1				1
Axillary folliculitis	1				1
Paronychia	1				1
Undiagnosed	1				

c.c. were each followed by flare-ups of the urticaria. On April 30, following twenty-eight injections of estradiol in olive oil with moderate improvement, we substituted, unknown to the patient, 0.2 c.c. of the olive oil vehicle in place of the estradiol in oil. Both of these substances look identical and were dispensed in identical vials. After one week of such "placebo" treatment, the patient complained of the return of a disturbing degree of urticaria. As a result she remained away from the clinic for one month.

The patient was seen again on June 2, and stated that she had been confined to bed with severe low backache, pelvic pain, and marked urticaria for the two-week period before and during menstruation (the two preceding menstrual periods had caused only moderate exacerbations of the urticaria). Hyposensitization was again started on June 4, using 0.1 c.c. of estradiol in olive oil. The dose was increased to 0.2 c.c. for a total of nine injections, with marked improvement of the patient's urticaria and general symptoms. The dose of estradiol in olive oil was gradually increased to 0.6 c.c., given intramuscularly, for a total of twenty-two injections in this series. In all, a total of fifty injections were given.

Upon completion of this series of injections, on August 11, 1947, the patient was markedly improved, and had only an occasional urticarial lesion. At no time was she denied the use of Pyribenzamine as a means of controlling excessive and intolerable itching. Whereas 400 mg. or more were taken prior to desensitization, only 50 mg. or less were used on completion of therapy. Subsequently the patient had no urticaria and took no Pyribenzamine; her menses were normal and without pain.

On January 26, 1948, we retested the patient with the following steroid hormones in olive oil (as previously used): cholesterol, estradiol, estrone, and progesterone, and with the olive oil vehicle alone. The twenty-four hour readings were negative, as were the forty-eight-hour readings with the exception of a poorly defined, faint erythema (2 by 1 cm.) at the estradiol in olive oil site. At this time a "recurrent test" was done by injecting 1.0 c.c. of estradiol in olive oil, subcutaneously in the right thigh. The patient reported that five hours after the injection, the estradiol in olive oil site began to itch and became intensely red and elevated and was about 1 by 2.5 inches in size. This reaction began to subside in about one-half hour. When seen on the following day, this same site was dusky-red and poorly defined (2 by 5 cm.). The patient did not have any urticaria as a result of the tests.

## CONTROL SUBJECTS

Skin tests with the hormone solution were carried out on sixty-four patients who had dermatoses apparently not related to menstruation or menopause (Table III), and who served as controls; thirteen gave questionable

and inconclusive responses of various types. Three were hypersensitive to the olive oil vehicle and were not included in the following statistics. Twelve patients gave questionable reactions to one or more test substances at twenty four hours alone or at both twenty-four and forty-eight hours. There were two patients presenting "retarded reactions." Two patients were tested for the "recurrent test reactions"; one of these, a man aged fifty-three, with an allergic eczematous contact-type dermatitis, gave a questionable positive to androsterone to which he had given a questionable reaction when first tested.

#### STUDIES WITH VARIOUS OIL SOLVENTS

Because of the difficulty of preparation of the neutralized olive oil, an attempt was made to find another suitable vehicle for testing with steroid hormones. Comparative studies were first made on the relative skin irritancy on cutaneous injection of sterile neutralized olive oil, sterile peanut oil and sterile sesame oil.

Twenty-five unselected patients from among those under treatment in the allergy department of the New York Skin and Cancer Unit were tested with the three oil preparations. An injection of 0.1 c.c. of each oil was given as previously described (at a level somewhat deeper than that usually used for intradermal testing). The tests were read after forty-eight hours with the following results: the neutralized olive oil and the peanut oil produced no reactions, while the sesame oil produced questionable reactions in two subjects. On the basis of these findings, it was decided to try peanut oil as the alternate solvent for the steroid hormones.

Thirty patients who presented dermatoses not apparently related to menstruation or menopause were divided into two groups of fifteen each. One group was tested with cholesterol, estradiol, estrone, and progesterone in olive oil in one arm, and with the same substances in peanut oil in symmetrically situated sites in the other arm. The second group was tested with testosterone, androsterone, and desoxycorticosterone acetate in olive oil and with the olive oil control in one arm, and with the same steroid hormones in peanut oil and with the peanut oil control in symmetrically situated sites in the other arm.

There was no case of sensitivity to olive oil in this group and only one instance of sensitivity to peanut oil, which developed three weeks after the tests were performed. One patient gave a questionable reaction to estradiol in both olive oil and peanut oil at the twenty-four-hour reading. Another gave questionable twenty-four-hour reactions to androsterone and desoxycorticosterone acetate also in both oil solvents. A third patient gave a positive reaction to desoxycorticosterone acetate in the peanut oil solvent.

From these tests we gained the impression that peanut oil solutions of the steroid hormones are suitable for cutaneous testing as far as lack of primary irritancy is concerned. Whether the reaction-producing capacity of olive oil and peanut oil solutions of steroid hormones is identical in patients

with skin hypersensitivity to steroid hormones must still be ascertained in suitable cases.

## COMMENT

Dermatoses as related to menstruation and menopause have been reported for many years, but Geber<sup>1</sup> is accredited with first demonstrating experimentally the presence of specific substances circulating in the blood of a patient at the time of the occurrence of menstrual urticaria. Blood serum obtained from a patient at the height of her menstrual urticaria would cause transient urticaria in this patient, but not in other women when injected intravenously during the intermenstruum. This patient could be desensitized by repeated intradermal injections of this serum,<sup>2</sup> whereas such desensitization could not be accomplished by administering the serum of a normal person. Positive skin reactions to extracts of menstrual secretion and probable successful hyposensitization with such extracts were reported by Salen.<sup>6</sup> It is interesting to note that the patient in our Case 1 had once been successfully hyposensitized by a procedure very similar to that used by Salen.

Aside from the work of Zondek and Bromberg, there are only few reports on skin tests for hypersensitivity to steroid hormones. Riebel reported a single case<sup>5</sup> having allergic coryza with premenstrual flare-ups who improved under treatment with folliculin (Theelin) administered subcutaneously, intranasally (nasal spray), or by vaginal suppository. Scratch tests done with folliculin were slightly positive to negative.

Sensitivity to Synapoidin (a combination of chorionic gonadotropin and anterior pituitary follicular stimulating hormone) was elicited by Phillips in a group of patients complaining of premenstrual headache.<sup>4</sup> Positive intradermal tests were reported using 0.02 c.c. of a 1:5 dilution of Synapoidin in 5 per cent glucose. Desensitization was accomplished by repeated intradermal injections of the test solution, gradually increasing the dose to 0.3 c.c. Phillips also found desensitization to be of value in premenstrual tension and premenstrual acne.

Three patients who developed purpura following estrogenic therapy were tested by Watson, Schultz and Wikott.<sup>11</sup> The test consisted of injecting intradermally 0.1 c.c. of 0.2 per cent suspensions of estrone and stilbestrol in physiological saline. The immediate skin test reactions were positive for estrone in one case, stilbestrol in another, and to both in a third case. Passive transfer tests were uniformly negative.

Among our patients complaining of dermatoses apparently related to menstruation or menopause who were tested, positive reactions were elicited in four of thirty-three, i.e., in about 12 per cent of the cases, as compared to 53 per cent with positive reactions in a similar series of dermatoses as presented in the table of the original workers.<sup>13</sup>

Numerous factors, however, must be considered which may account for the rather wide variation in results. In their concluding comment,<sup>13</sup> Zondek

and Bromberg stated: "The high level of the incidence of endocrine allergy in the cases reported above results from case selection and should not be regarded as forming evidence that endocrine allergy is a frequent occurrence. The cases we have described were all selected from a group which had proved resistant to all common methods of treatment, and in which the symptoms of the complaint related to the genital function. For general practice, endocrine allergy is not often encountered." The patients tested in our series, whose complaints were apparently related to genital function, do not fulfill these rigid criteria of selection. Whereas histories were carefully elicited from the patients tested to make certain that the dermatosis was related to menstruation or menopause, it is possible that prolonged study might have revealed some cause unrelated to genital function. Nor had all of our cases run the gamut of common methods of treatment, i.e., we have no proof that they would "have proved resistant to all common methods of treatment."

With the exceptions of the two cases reported above in detail, only skin reactions which we ourselves observed have been included in this report. Yet the statements of patients concerning reactions which they noted leads us to suspect the occurrence in some instances of "retarded reactions" as well as delayed sensitivity to the olive oil solvent. It is possible that had we had the opportunity to follow and retest more of the patients giving questionable reactions, there would have been a higher incidence of subjects in whom hypersensitivity to endocrine substances could have been established.

Moreover, evaluation of the test responses was not always a simple matter, because of the numerous questionable reactions which occurred in the patients presenting dermatoses apparently related to genital function, as well as in the control group. Some of the questionable reactions which occurred despite all precautions taken might be accounted for by the accidental deposition of the test substance in the epidermis and upper cutis, thus causing a nonspecific oil reaction; after 0.1 c.c. of the oily solution was injected and the needle withdrawn, it was not unusual to note a minute backflow of the oil to the surface of the skin. Rubbing of a negative test site, e.g., mechanical irritation of a site caused by a tight dress sleeve, ornamental jewelry, handbag, or packages carried in the arms, in some cases produced a localized erythema which could be misinterpreted for a positive reaction.

Although the factors mentioned may account for some of the questionable or false positive responses, they do not explain all the bizarre reactions which occurred, such as (1) questionable reactions at twenty-four hours with negative reactions at forty-eight hours and with negative "recurrent tests," (2) positive or questionable reactions to olive oil at twenty-four hours, without similar reactions at any of the other sites which had been injected with olive oil containing steroid hormones, (3) the premenstrual flare of several test sites in one of the patients with a dermatitis apparently



related to menstruation, (4) control patients giving "retarded reactions" with a positive reaction at one site and questionable reactions at several other test sites.

We believe that many of the difficulties encountered in evaluating the method of Zondek and Bromberg are due to the use of oil as the vehicle for the steroid hormones. The nonspecific reactions which are inevitably produced when olive oil is injected intradermally necessitated the deposition of the test materials at a deeper level than is customary in orthodox skin testing for the urticarial and tuberculin-type responses. We have used the name "cutaneous" tests since the skin level at which these tests have been performed is neither intracutaneous nor subcutaneous but intermediate between these. The necessity for injecting deeper than usual means a diminished contact of the test materials with the blood vessels and other structures of the upper cutis which may be the principal shock tissue in the orthodox wheal and tuberculin-type responses. Moreover, it stands to reason that the release of the allergenic materials from olive oil solutions takes place at a much slower rate than the release of allergenic materials from aqueous solutions. Obviously these factors can account not only for some of the difficulties encountered in the evaluation of the responses elicited but, perhaps even more important, the type of response seen in these tests. For the reactions, described by Zondek and Bromberg in a large series of cases and confirmed by us in a few dermatologic cases, do not fit in with any of the classical immunologic skin responses, i.e., the urticarial, tuberculin-type and eczematous reactions. Rather these responses are either a type of skin response not hitherto described or they are a type of response which is intermediate between the urticarial and the tuberculin-type responses. Our limited experience with positive reactions in these tests leads us to believe that this is not an entirely new type of cutaneous reaction but only a "crossing" between the urticarial and tuberculin-type responses, due to the use of oil as the vehicle for the allergen and the deposition of the allergenic materials relatively deep in the skin.

In our clinical material of dermatologic cases "related to genital function," the tests for hypersensitivity to endocrine substances led to positive results in only a few cases. Based on these results this new method would not appear to be promising as a *routine* investigative procedure for large series of cases. However, the positive test results observed in a few cases and the encouraging results of specific therapy, instituted in two cases on the basis of the test results, indicate that the method of Zondek and Bromberg deserves further trial in properly selected cases.

#### SUMMARY AND CONCLUSIONS

1. Cutaneous tests for hypersensitivity to steroid hormones according to the method of Zondek and Bromberg were performed in 102 dermatologic patients.
2. Among the thirty-eight patients whose dermatoses were apparently

related to genital function (menstruation, menopause) there were four who gave positive skin responses. In two of these (both cases of urticaria) hyposensitization was carried out with the hormone which had elicited the positive skin response and was followed by very marked clinical improvement. In eleven additional patients questionable and inconclusive responses were elicited.

3. Among the sixty-four control patients whose dermatoses were *not* related to genital function, no positive skin reactions were seen. In thirteen of these patients questionable and inconclusive responses were elicited.

4. Screening tests suggested that it may be possible to substitute peanut oil for the specially prepared olive oil as a vehicle for the steroid hormones.

5. The skin responses elicited in these tests were different from the classical types of immunologic skin reactions, and suggest a form of response intermediate between the urticarial and tuberculin-type response. This unusual type of skin response is attributed to the use of oil as a vehicle and to the relatively deep deposition in the skin of the test materials.

6. Tests for hypersensitivity to steroid hormones (method of Zondek and Bromberg) are, in our opinion, not suitable for routine diagnostic use. However, in a certain number of carefully selected cases, related to genital function, this method has definite merits. Hyposensitization in urticaria cases with positive tests to steroid hormones is a promising procedure.

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## FEVER DUE TO FOOD ALLERGY

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THIS paper reports food allergy as one cause of "unexplained fever."\* Fever due to drug and serum allergy is generally recognized. Very occasionally, fever also arises from allergy to pollens or other inhalants, as reported by Rowe<sup>13,18</sup> and Urbach. Though fever due to food allergy was first reported by Barnathan<sup>2</sup> in 1911 and by Laroche, Richet, and Saint-Girons<sup>9</sup> in 1919, and has been reported by other observers<sup>1,5-8,18,19</sup> since then, its general recognition has been too long delayed.

Failure to recognize food allergy as one cause of fever accounts for some unjustifiable diagnoses of idiopathic or psychogenic fever, subclinical tuberculosis, brucellosis or other questionable infections. It has led to unnecessary operations on tonsils, appendices, gall bladders and pelvic organs. Needless surgical intervention has been performed on nasal sinuses because of the association of fever with nasal congestion, blocking or postnasal mucus, and especially with swollen membranes or opacities in the antra or other sinuses which were not due to infection but to allergy, especially to foods. Such fever often has constituted the chief reason for prolonged, unnecessary inactivity or vacations, for bed rest in hospitals or sanatoria, and for extensive clinical and laboratory investigations.

The following case report illustrates the occurrence of prolonged allergic fever that was preceded by a life-long anorexia, aversion for milk, and recent colonic symptoms due to food allergy. Because of this fever, the patient was hospitalized for four and one-half months; during this time many laboratory and clinical investigations were conducted, and at one time a presumptive diagnosis of psychogenic fever was made. This case is of special interest because in the record is contained the only chart of a course of fever due to food allergy that as yet has been published.

### CASE REPORT

A girl, aged eighteen, developed fatigue and anorexia in July, 1942. Gradually, intermittent cramping arose in the mid-abdomen and rectum. By the middle of August there was watery diarrhea with afternoon fever and an elevation in temperature to 102° F. The administration of succinyl sulfathiazole for two weeks had no effect on the fever. On September 19, she was then hospitalized and her problem studied for about a month. Proctoscopic examinations revealed an easily bleeding and slightly inflamed mucosa. Laboratory studies and physical examination (Table I) revealed no cause for the continued fever. She was sent, on October 12, to another hospital where she remained for three and one-half months at complete rest. Figure 1 shows the frequency, variation and degree of temperature that was associated with the fever. In the four and one-half months of hospitalization, she passed from one to four stools a day; these were soft and at times semi-fluid.

\*Hypothermia also results from allergy, especially during anaphylactic shock.

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TABLE 1. SUMMARY OF PREVIOUS TREATMENT AND LABORATORY STUDIES IN CASE ONE

Stools were soft or liquid, 1 to 3 a day during hospitalization.

Pulse rate varied in the morning between 75 and 90 and in the afternoon between 110 and 130 when fever was present.

With the control of food allergy, the afternoon pulse rate fell to 90 to 100.

Vitamin B complex was given subcutaneously, 1 to 2 c.c. every two days.

Sulfadiazine, 6 gm. daily, was given from November 23, to December 6. (Blood level, 12.6 mg. per cent.)

Aspirin, 10 gm. twice daily, was given from December 31 to January 27.

## BLOOD COUNTS

Date	Hemo- globin (Meth- od?)	Red Cells x 1000	White Cells	Total Poly- morpho- nuclears	Differential, PMN's		Lympho- cytes	Large Mono- nuclears	Eosino- philes	Baso- philes
					Banded	Seg- mented				
9-20-42	69	4250	9100	84			14		2	
10- 6-42	71	3960	7600	81			14	3	2	
10-15-42	79	4900	8500	52	44	8	37	8	2	1
10-30-42	71	4260	8100	61	33	28	18	7	13	1
11- 4-42	71	4460	7500	65	43	22	18	9	6	2
11-12-42	71	5000	6900	65	56	9	22	3	9	1
11-18-42	74	5150	9250	57	42	15	24	9	10	
11-23-42	76	5300	10470	67	51	16	20	3	10	
11-27-42	76	5300	7350	74	58	16	14	6	6	
12- 7-42	83	4900	4800	58	48	10	24	8	10	
12-14-42	78	5300	5200	59	40	19	22	5	12	2
12-31-42	73	4910	4570	64	60	4	18	7	9	2
1-19-43	64	4900	5700	54	40	14	27	5	14	
1-25-43	90	5340	6400	41	18	23	27	9	23	
2- 8-43	70		5850	55	22	23	30	8	7	
2-15-43	68		5400	60			25	9	4	2
5-19-43	70	5190	6750	72			20	5	2	1

## LABORATORY STUDIES

Urine analyses: 10 complete ones, negative.

Stool culture (9-21-42): negative.

Blood culture (9-21-42): negative.

Stool examination for ova and parasites: negative.

Blood examination for malaria: negative.

Tuberculin, 1-2,000 O.T.: negative.

Coccidioidin skin test, 1-100: negative.

Serum agglutination tests for typhoid, paratyphoid A and B, brucella on three occasions were negative; for abortus, S. Supestifer, on two occasions were negative. Complement fixation test for brucella was negative.

Heterophile agglutination: negative.

X-ray of chest and sinuses: negative.

X-ray of colon: negative.

Sedimentation Rates:

9-20-43—30 minutes—18 mm.

10- 1-43—37 minutes—18 mm.

10-14-43—60 minutes—25 mm. (normal 10)

7- 2-44—60 minutes—10 mm.

Vitamin B complex, 1 to 2 c.c., was injected intramuscularly every two days during most of this period. Sulfadiazine, 6 gm. daily, was given from November 25 to December 6, with no definite effect on the fever. Finally, aspirin, 10 gr. two times a day, was given from December 31 to January 27, and resulted in intermittent lowering of the fever. Throughout her entire illness, when her temperature was elevated above 101° F. and especially over 102.5° F., there was at times chilling with "goose flesh" reactions. There were night sweats which varied with the amount of fever. However, no headache or generalized aching occurred. In November a small fissure was discovered at the posterior commissure of the anal aperture, and later an induration, 2 by 4 cm., was discovered in the left wall of the lower rectum. This was incised on December 11, but produced no reduction in the fever.

The patient was referred to the writer by Dr. Karl F. Meyer on January 29, 1943. Food allergy, especially for milk, was suspected immediately for the following reasons: the patient stated emphatically that she never had liked milk. It had been forced upon her in childhood and since then had been taken only when flavored, or in ice cream, sherbets or in cooking. The patient, according to her mother, always

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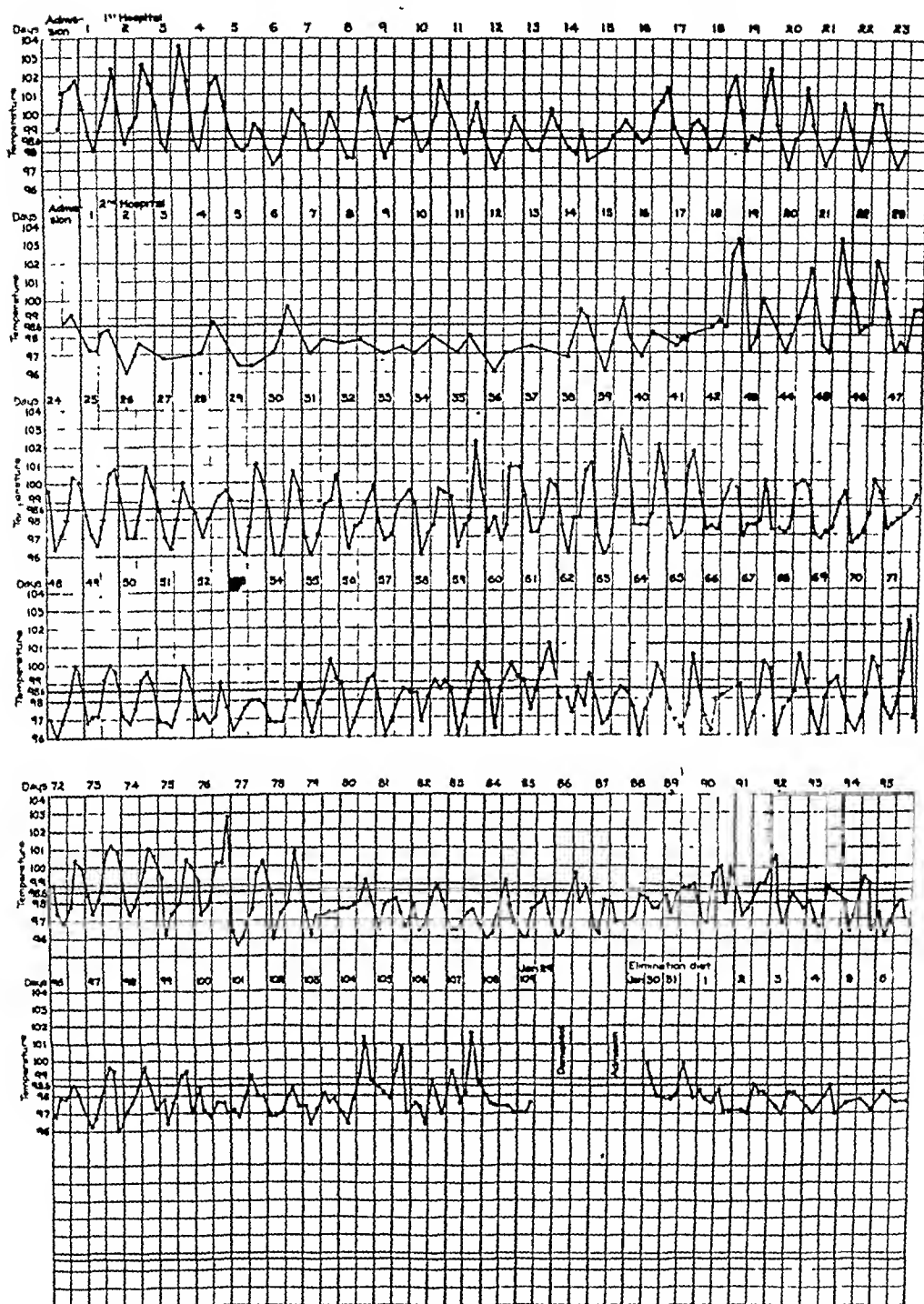


Fig. 1. Temperature chart in three hospitals.

had been finicky about her food; she had been spoon-fed entirely up to the age of six years. Until this time all foods apparently had agreed with her. During the hospitalization for four and one-half months, the mother had spoon-fed her on most evenings because of anorexia; several glasses of milk, cream and butter in desserts and cooking had been included in her daily diet. With the exception of a

life-long lack of appetite and energy, the patient gave no previous history of gastrointestinal symptoms nor of any other allergic manifestations or chronic illness. There was no familial history of allergy.

The following reactions were obtained with the scratch test with eighty-five food allergens: coconut 2-plus; peanut 2-plus; pecan 1-plus; black walnut 1-plus; English walnut 1-plus. With the intradermal test, the following reactions occurred: wheat, coffee, and peach gave questionable reactions; string beans 2-plus; tomato 2-plus; white potato 2-plus; prune 1-plus; grapefruit 1-plus. It is of interest that the scratch and intradermal tests with milk were negative.

Because of the possibility that the fever, fatigue, colonic symptoms, the long standing finickiness for foods and anorexia were due to food allergy, she was placed on the writer's cereal-free elimination diet.<sup>18</sup> As may be seen in the chart, her fever disappeared in twenty-four hours. During the next four days she was allowed to increase her activity, and in one week she walked out of the hospital, fever-free and symptom-free. Her appetite and energy gradually increased, to become greater than at any time in her life. In three weeks her weight had increased from 108 to 119 pounds, and in three more weeks she weighed 124 pounds. In the next five months all foods, one by one, were added. On February 26, she drank ounce of milk and increased the amount to 2 ounces on the next day. On the third day her abdomen felt full and distended, and her anal tissues were sore and inflamed. That evening, for the first time since the second day of the elimination diet, her temperature was 99° F., and the following evening it was 99.2° F. The abdominal and anal distress gradually disappeared during the next seven days. Since then, similar symptoms and mild fever have reappeared when milk, even in small amounts as in a doughnut or candy, has been ingested. Chocolate, to a lesser degree, causes the fever and colonic distress. By August her weight had increased to 132 pounds. At present, in 1948, she still cannot tolerate milk without resultant fever and rectal and anal distress. She is well and free of fatigue and weighs 136 pounds.

When the writer first saw the patient there was a muco-purulent discharge from the anus. Proctoscopic examination revealed an ulcer about 1 inch in diameter at the anorectal margin. The ulcer was removed by surgical procedure and was followed by rapid healing. In spite of the ulcer, her temperature remained normal as long as the allergenic foods were absent from the diet.

The allergic fever was of the persistent type and was present daily during her four and one-half months of hospitalization, except for twelve days during the first two weeks in the second hospital and again for twelve days on and off during the last twenty-nine days in the hospital. As will be discussed later, temporary refractoriness or desensitization best explains the first period of normal temperature. The effect of aspirin, 10 grains twice a day, given from the seventy-ninth to the one hundredth and ninth day, probably accounts for intermittent normal temperature in the latter period. It is interesting that the morning temperature failed to fall to 97° F. during the first nineteen days, in comparison to its frequent fall to 97° F., and even to 96° F., thereafter. Since the relief of her food allergy, the morning temperature has not been below 97° F.

#### DISCUSSION

Milk allergy was the main cause of the allergic fever and the colonic and anal allergy. Chocolate seemed to be a minor cause. Peanuts and walnuts caused moderate colonic distress. Milk is the food which probably is the most frequent cause of allergic fever and is a common cause of gastrointestinal allergy, especially in the colon.<sup>17</sup> Other foods always must be suspected, particularly those excluded from the writer's elimination diets.

The life-long history of aversion to milk in this patient emphasizes the importance of a carefully recorded dietary history. Although allergy is not always responsible for food dislikes and disagreements, such history always requires the proper study of food allergy. Because of the frequency of food allergy, a dietary history indeed should be routine in practice.

The fallibility of the skin test,<sup>15,20</sup> especially for food allergy, is illustrated by several positive reactions which caused no clinical symptoms and the negative reaction to milk, even intradermally, which caused such definite allergy in this patient.

Because of this fallibility of the skin testing and the usual allergy to more than one or two foods, the writer's usual routine is to study with his elimination diets<sup>18</sup> those patients who are suspected of having food allergy; this is modified by a history of definite food disagreements or dislikes and by positive reactions to foods obtained by the scratch method. Thus, in this patient, the writer's cereal and fruit-free elimination diet was utilized. Fruit was excluded since it is a common cause of allergy in all parts of the gastrointestinal tract. When the fever and the colonic symptoms in this patient had been absent for two weeks, other foods were added, each being tried for three or four successive days before another was added. With the inclusion of milk, the fever and colonic symptoms recurred, as noted above. Peanuts, walnuts and chocolate also produced colonic distress and moderate diarrhea.

During this period of study of possible food allergy, the total elimination of excluded foods is required because a maximum degree of allergy always must be assumed until the symptoms are relieved. Then the degree of allergy to the causative foods can gradually be determined by feeding tests. Thereafter, partial or total exclusion of the food can be continued as required for relief. The maintenance of nutrition, while the elimination or any trial diet is being used, has long been emphasized by the writer because of the necessity to use the diet for more than a few days in most cases and the usual necessity for subsequent elimination of proven allergenic foods for months or years to obtain relief of symptoms. Prolonged diet trial is especially necessary for the study of food allergy as a cause of cyclic recurrent manifestations with intervening days or weeks of freedom.

The persistent allergic fever, in this case, disappeared in two days after the elimination of the allergenic foods, which is in contrast to the less rapid disappearance of such fever in other similar patients studied by the writer. This varying speed of relief of fever and other manifestations of food allergy may depend on the persistence of the specific reacting bodies or of the food allergens in the blood and tissues after the total elimination of the allergenic foods. Moreover, the cellular and tissue changes resulting from the specific allergic reactions require varying times for restitution to normal after the proper diet has been instituted.

In contrast to the persistent type of fever which usually results from

food allergy, the writer soon will report the recurrent allergic fever which may occur with cyclic attacks of bronchial asthma or symptoms of gastrointestinal allergy and less often with other recurrent manifestations of food allergy. The normal temperature between these periods of recurrent allergic fever is comparable to the relief of other symptoms after recurrent attacks of other allergic manifestations, including bronchial asthma, allergic headache, symptoms of gastrointestinal allergy, intermittent hyarthrosis, or other cyclic manifestations of food allergy. The allergenic food or foods usually are common ones eaten every day. The duration and severity of the fever or other symptoms probably depend on the accumulation of the specific reacting bodies in the cells of the shock tissues and their exhaustion during the reactive period. Persistent fever and other symptoms due to food allergy, on the contrary, may be attributed to the failure of the shock tissues to become desensitized or refractory to the causative allergens.

Chilling and goose flesh with rising fever and night sweats upon retiring or through the night often occur from food allergy. Children with allergy may perspire soon after retiring, especially over the head and neck, even when lightly covered. Night sweats due to chronic food allergy and not accompanied by fever in children and adults have been observed by the writer.

Food allergy should be considered as a cause of fever when the physical examination and laboratory studies give no explanatory clues, and especially when treatment based on positive findings gives no relief. As in other possible clinical allergy due to food, this study is especially necessary if the patient has a personal history of other allergic manifestations and/or a familial history of allergy. Thus, in this case, the aversion to milk and the probable colonic allergy stressed the study of food allergy as one cause of the fever. The fever may be of major or minor consequence. The absence of any familial allergy did not detract from this necessity.

During the four and one-half months before the writer saw the patient, infections of all types had been sought for as evidenced by the many blood counts, agglutination tests, blood cultures, stool examinations and other tests recorded in Table I. The absence of leukocytosis or of an increase in the polymorphonuclear cells, except in the first two counts, is to be noted, though leukocytosis may occur, especially in children with uncontrolled allergy. The rapid sedimentation rates, apparently due to food allergy in this patient, are of interest. The tendency to an increasing blood eosinophilia should have suggested allergy in this patient. With control of the food allergy, the eosinophilia and rapid sedimentation rate disappeared. Trichinosis also had been considered because of the eosinophilia.

The relief from her fever, from the colonic and anal symptoms, and from the fatigue and the other toxic symptoms by use of the elimination diet, and their subsequent reproduction by the ingestion of milk, prove



that food allergy was responsible. Her initial colonic symptoms suggested the onset of a possible chronic ulcerative colitis, which, in the writer's opinion, is frequently due primarily to food allergy<sup>17</sup> (several cases due to pollen allergy also have been studied). The easy bleeding and mild inflammation of the mucosa, however, only were demonstrated during several proctoscopic examinations. The recurrence of the colonic and anal distress on a few occasions when milk has been taken since the original control of her allergic fever five years ago, emphasizes the persistence of the allergic reactivity in these tissues. If the allergy had not been recognized, more definite tissue changes due to chronic ulcerative colitis might have developed.

As soon as the allergic fever and the colonic and toxic symptoms<sup>10,11,12,14</sup> were relieved with the elimination diet, the patient for the first time in her life ate with avidity and willingness and evidenced normal energy, enthusiasm and nervous stability. It is noteworthy that a steady gain of weight up to 26 pounds in the first six months of allergic supervision occurred with an entirely milk-free diet. In this patient anorexia was due in food allergy alone.† Milk was excluded from the diet without nutritional damage inasmuch as calcium was given and an adequate protein and caloric intake were maintained.

The most likely explanation of allergic fever is a disturbance in the temperature-regulating center of the brain by a localized or generalized allergic reaction. The following less likely possibilities may be mentioned. The allergic reaction in the shock tissues might produce fever. Again, the allergic reaction in nasal, bronchial or gastrointestinal mucosa, especially if severe and explosive in type, might encourage the rapid growth of otherwise quiescent bacteria. The rapid relief of fever in this patient with the exclusion of milk rules out infection as a cause.

#### CONCLUSIONS

1. Food allergy as one cause of "unexplained fever" must be recognized. Although any food may be responsible, milk is the common offender.
2. Failure to consider allergic fever accounts for needless surgical operations performed because of possible foci of infection or other lesions, and also for the unnecessary bed rest in home, hospital, or sanitarium.
3. Other manifestations of food allergy of varying severity may accompany allergic fever.
4. Chilling and night sweats often occur. Night sweats, moreover, may result from chronic food allergy in the absence of allergic fever.
5. Leukocytosis, eosinophilia and a rapid sedimentation rate may or may not be present.
6. Allergic fever due to food allergy may occur in recurrent attacks: usually it is persistent and somewhat varying in degree.

†Chronic food allergy is a common cause of anorexia, not only in children but also in adults.

7. One case of fever due to food allergy associated with allergic toxemia and colitis, with the recorded temperature during hospitalization for 122 days before allergy was suggested as one possible cause, is reported and discussed. This graphic record of prolonged fever due to food allergy is the first of its kind in the literature.

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## MOLD DISTRIBUTION IN AIR AND DUST IN KENTUCKY

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EXCEPT for the survey made in Louisville, Kentucky, by the Committee on a Pollen Survey of the United States for the Society for the Study of Asthma and Allied Conditions in 1942 (Vander Veer et al<sup>28</sup>), no extensive studies of mold distribution in Kentucky have been reported. A survey has been made, therefore, of the distribution of molds in outdoor air, indoor air, and in house dust, in eastern Kentucky and in central and western Kentucky.

Two quantitative surveys were made, one in January and the other in March.

For the primary isolation of the molds, the plate method with Anderson's<sup>1</sup> modification of Sabouraud's medium was employed, except that the medium was adjusted to the desired pH (3.0) with N/1 H<sub>2</sub>SO<sub>4</sub> instead of N/1 HCl, after sterilization in the autoclave.

Dehydrated Bacto-potato-dextrose agar, adjusted to pH 5.6, was used for subculturing the molds from the plates and for maintaining stock cultures of the isolates.

Poured plates of the above plating medium, which had been sealed with scotch tape until ready for use, to prevent drying, were exposed on the same day in each of the following places: Ashland, Catlettsburg and Middlesboro in eastern Kentucky; Covington, Independence, Lexington, Nicholasville and Coakley in central Kentucky; and Kevil in western Kentucky. On January 1, 1946, co-operators at each location away from Lexington, and we in Lexington, exposed one plate outdoors and one plate indoors for fifteen minutes. The plates were resealed with scotch tape and the ones away from Lexington were returned on January 3. On January 1 each co-operator, as well as we in Lexington, also collected a sample of house dust in a sterile test tube.

All the exposed plates were incubated at room temperature for from three to seven days. Each sample of house dust was plated on Sabouraud's medium by streaking the plates with a loopful of the dust. These plates were also incubated at room temperature for from three to seven days.

The colonies of each type of mold, as determined by macroscopic appearance, were counted, and a representative of each type was subcultured on potato-dextrose agar slants. Two sets of stock cultures were made from each type.

For the identification of the molds, moist chamber preparations of the

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Presented at the third annual meeting of the American College of Allergists, at Atlantic City, N. J., June, 1947.

organisms, incubated at room temperature, were studied daily under the 16 mm. and 4 mm. objectives of the microscope.

The identification and classification of the cultures were made in accordance with the criteria set forth in Gilman's *Manual of Soil Fungi*.<sup>13</sup>

The survey in March was carried out in the same manner as the one in January, except that Pikeville, in the eastern part of the state, was included in the survey.

Table I shows the results of the January survey. Representatives of the following genera of molds were found: *Alternaria*, *Aspergillus*, *Cephalosporium*, *Hormodendrum*, *Penicillium*, *Phycomyces*, *Rhizopus*, and *Tilachlidium*. The species of the genus *Penicillium* were the most widely distributed and the most numerous. Only a few of the species of this genus were identified. These were *Penicillium citrinum*, *Penicillium frequentans*, *Penicillium notatum*, and *Penicillium spinulosum*.

Other species of the *Fungi Imperfecti* that were identified were *Alternaria geophila*, *Alternaria humicola*, *Alternaria tenuis*, *Aspergillus luchuensis*, *Aspergillus versicolor*, *Cephalosporium acremonium*, *Hormodendrum cladosporioides*, *Hormodendrum nigrescens*, and *Hormodendrum olivaceum*. Of these, *Aspergillus luchuensis* and *Hormodendrum nigrescens* were the most numerous and the most widely distributed.

The only species of the *Phycomycetes* that was identified was *Rhizopus nigricans*.

Table II shows the results of the March survey. In addition to all the genera of molds found in January, *Macrosporium*, *Monotospora*, *Mucor*, *Oospora*, *Stemphylium* and *Tetracoccosporium* were also found. Members of the *Penicillium* genus were again the most widely distributed and the most numerous.

The following species of the *Fungi Imperfecti* were identified: *Alternaria humicola*, *Alternaria tenuis*, *Aspergillus fumigatus*, *Aspergillus luchuensis*, *Aspergillus niger*, *Aspergillus versicolor*, *Aspergillus tamarii*, *Cephalosporium acremonium*, *Hormodendrum cladosporioides*, *Hormodendrum hordei*, *Hormodendrum olivaceum*, *Hormodendrum viride*, *Macrosporium commune*, *Monotospora brevis*, *Oospora variabilis*, *Penicillium citrinum*, and *Stemphylium macrosporoideum*.

*Mucor piriformis*, *Rhizopus nigricans*, and unidentified species of *Mucor* and *Phycomyces* represented the *Phycomycetes*.

Of the species identified, the most important, from the standpoint of distribution and numbers, were *Alternaria tenuis*, *Aspergillus luchuensis*, and *Hormodendrum cladosporioides*.

In Figure 1, parts of the data from Tables I and II have been summarized to show a comparison of the results of the January and March surveys in eastern Kentucky. The March survey yielded a higher percentage of *Aspergillus*, *Hormodendrum*, and *Tilachlidium*, a lower percentage of *Penicillium*, and an equal percentage of *Cephalosporium*, *Oospora*, *Mucor*, *Rhizopus*, *Tetracoccosporium*, *Alternaria*, *Macrosporium*,

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TABLE 1. DISTRIBUTION OF MOLDS IN OUTDOOR AIR, INDOOR AIR, AND HOUSE DUSTS IN KENTUCKY DURING JANUARY, 1946

Molds	Ashland (NE)			Cattletown (NE)			Middlesboro (SE)			(SC)			(NC)			Totals														
	1*	2†	3‡	1	2	3	1	2	3	1	2	3	1	2	3															
<i>Alternaria</i> <i>geophila</i>																6														
<i>humicola</i>																12														
<i>tenella</i>																28														
Sp																1														
<i>Aspergillus fumigatus</i>																42														
<i>faustus</i> group																38														
<i>lichuanus</i>																10														
<i>niger</i>																4														
<i>versicolor</i>																1														
<i>tanarii</i>																2														
Sp																5†														
<i>Cephalosporium veronumum</i>																1														
<i>Hormotendrium chadosporoides</i>																3														
<i>hordii</i>																1														
<i>nigrescens</i>																3														
<i>olivaceum</i>																6														
<i>viride</i>																2														
<i>Macrosporium commune</i>																9														
<i>Monospora brevis</i>																2														
<i>Mucor puriformis</i>																3														
Sp																6														
<i>Oospora variabilis</i>																3														
Sp																1														
<i>Penicillium citrinum</i>																3														
<i>frequentans</i>																17														
<i>notatum</i>																18														
<i>spinosum</i>																39														
Sp																3														
<i>Phycomyces</i> sp																1														
<i>Rhizopus nigricans</i>																61														
<i>Stemphylium microsporioides</i> im																31														
<i>Tetracosporium</i> sp																49														
<i>Tillichium</i> sp																21														
Unidentified																10														
Totals	2	5	13	16	10	21	49	37	76	4	32	4	41	50	27	28	0	102	41	79	97	3	81	22	3	4	0	4	122	975

\*Number of colonies found on plates exposed outdoors for fifteen minutes  
†Number of colonies found on plates exposed indoors for fifteen minutes  
‡Number of colonies found on plates streaked with one loopful of house dust

TABLE II. DISTRIBUTION OF MOLDS IN OUTDOOR AIR, INDOOR AIR, AND HOUSE DUSTS IN KENTUCKY DURING MARCH, 1946

[illegible]

May-June, 1948

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and *Stemphylium* were found only in March, while *Phycomyces* was found only in January.

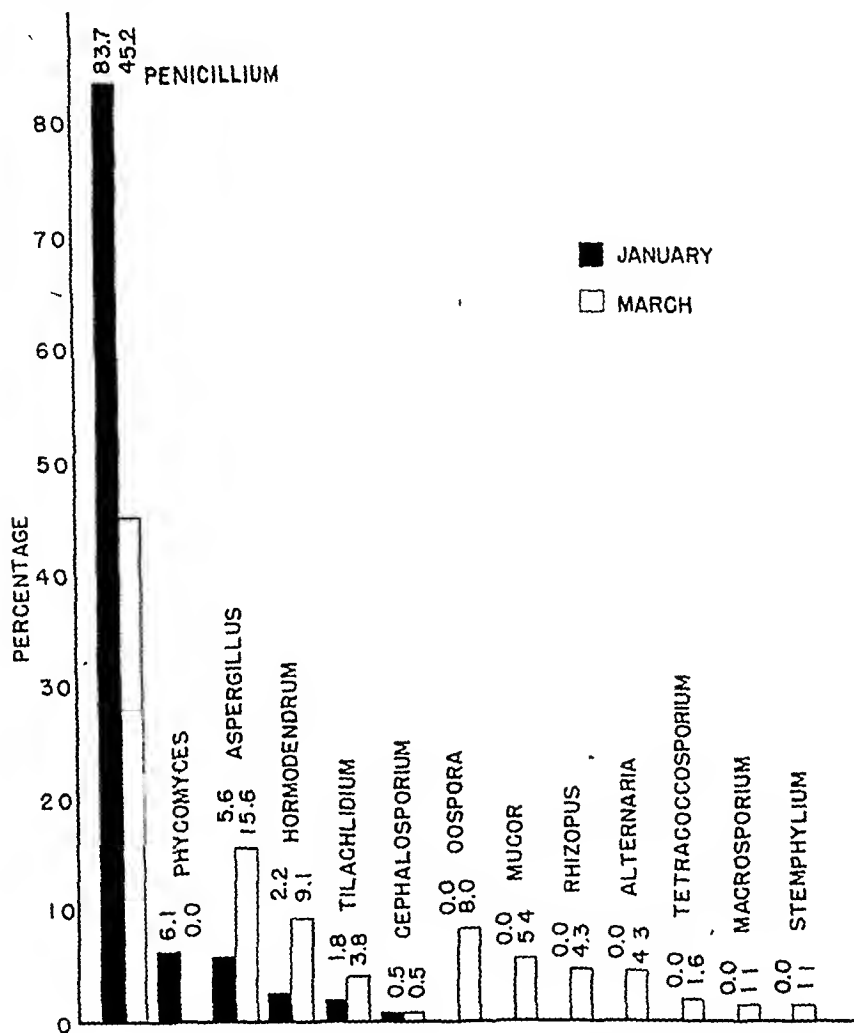


Fig. 1. Comparison of genera of molds found in eastern Kentucky during January and March, 1946.

In Figure 2, parts of the data from Tables I and II have been summarized to show a comparison of the results of the January and March surveys in central and western Kentucky. In this section, too, the March survey yielded a lower percentage of *Penicillium* and *Phycomyces* and a higher percentage of *Aspergillus* and *Hormodendrum*. It also yielded a higher percentage of *Alternaria*, *Cephalosporium*, and *Rhizopus*. The March survey yielded a wider variety of molds. In addition to all the genera found in January, *Oospora*, *Tilachlidium*, *Monotospora*, and *Mucor* were also found.

If Tables I and II are referred to again, it will be seen that certain species of molds were found entirely in March, others almost entirely in

March and one species only in January. *Hormodendrum hordei*, *Hormodendrum viride*, *Aspergillus fumigatus*, and *Aspergillus niger* were found

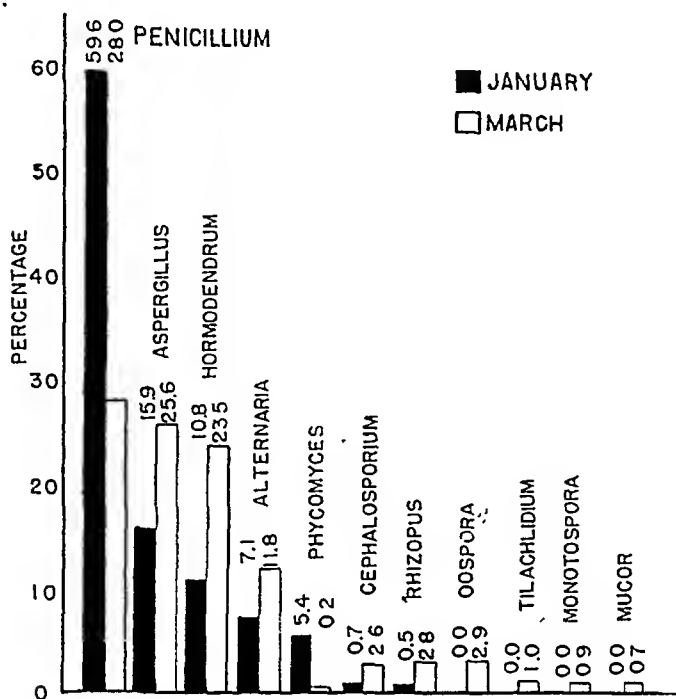


Fig. 2. Comparison of genera of molds found in central and western Kentucky during January and March, 1946.

entirely in March. *Hormodendrum cladosporioides* and *Alternaria tenuis* were found almost entirely in March while *Hormodendrum nigrescens* was found only in January.

In Figure 3, parts of the data from Tables I and II have been summarized to show the comparison of the results of the surveys in central and western Kentucky with the results of the surveys in eastern Kentucky. Central and western Kentucky yielded higher percentages of *Aspergillus*, *Hormodendrum*, *Alternaria*, and *Cephalosporium*, while eastern Kentucky yielded higher percentages of *Penicillium*, *Oospora*, *Tilachlidium*, and *Mucor*. *Phycomyces* and *Rhizopus* were approximately equally prevalent in the two localities. *Tetracoccusporium*, *Macrosporium*, and *Stemphylium* were found only in eastern Kentucky; *Monotospora*, only in central and western Kentucky.

*Penicillium* was found to be the most prevalent mold genus throughout the state.

The list of genera found in Kentucky does not differ materially from those reported from other sections of the country. Table III lists the surveys of air-borne molds that have been made in the United States. The



localities in which the surveys were made, the year, the investigators, and the molds found are recorded. Table IV lists all the mold genera that have been reported in these surveys and the number of investigators by

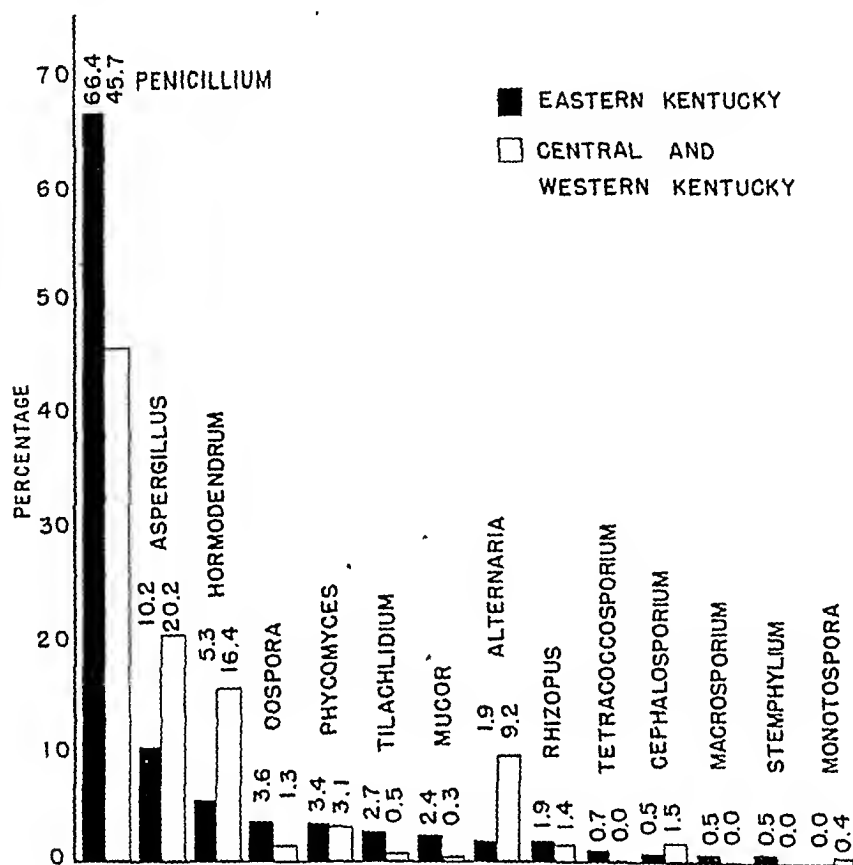


Fig. 3. Comparison of genera of molds found in eastern Kentucky with those found in central and western Kentucky during January and March, 1946.

whom they were reported. Listed in this table also, for comparison, are the mold genera found in our survey in Kentucky. It may be seen from this table that of the genera reported in other parts of the country, we failed to find *Monilia*, *Trichoderma*, *Helminthosporium*, *Cladosporium*, *Monosporium*, *Fusarium*, *Chaetomium*, and *Spondylocadium*. Of greater significance, perhaps, is our finding of four genera that had not been reported from any of the other sections of the country. These genera are *Monotospora*, *Stemphylium*, *Tetracoccosporium*, and *Phycomyces*.

In Table V the data have been summarized to show the distribution of molds in outdoor air, indoor air, and house dusts. *Alternaria* was found most frequently in outdoor air, comprising 17.8 per cent of the total molds from that source, 10.6 per cent of those from indoor air, and only 1.5 per cent of those from house dusts. *Aspergillus* was found most frequently in house dusts, comprising 23.9 per cent of the total molds from that source, 17.5 per cent of those from indoor air, and only 1.3 per cent of

# MOLD DISTRIBUTION IN KENTUCKY—NEWTON ET AL

TABLE III. SURVEYS OF AIR-BORNE MOLDS IN THE UNITED STATES

Locality	Year	Investigator	Molds Found
Baltimore, Md.	1932	Patterson and Gay <sup>19</sup>	Mucor, Rhizopus, Penicillium, Aspergillus
Oklahoma	1932	Balyeat, Stenen, and Taft <sup>2</sup>	Aspergillus, Penicillium
Galveston, Texas	1934	Prince, Selle and Morrow <sup>23</sup>	Monilia, Penicillium, Aspergillus, Trichoderma, Helminthosporium, Cladosporium
Boston, Mass. up to 19,600 ft. (aeroplane)	1934	Proctor <sup>24</sup>	Aspergillus, Penicillium, Cladosporium, Alternaria, Helminthosporium, Monilia, Trichoderma
Boston, Mass. up to 20,000 ft. (aeroplane)	1935	Proctor <sup>25</sup>	Aspergillus, Penicillium, Rhizopus, Mucor, Oospora, Monosporium, Macrosporium, Tilachlidium, Fusarium
Chicago, Ill.	1936	Feinberg <sup>11</sup>	Aspergillus, Penicillium, Alternaria, Hormodendrum
Chicago, Ill.	1936	Feinberg and Little <sup>12</sup>	Alternaria, Penicillium, Aspergillus
Washington, D. C.	1936	Brown <sup>6</sup>	Alternaria, Aspergillus, Penicillium
Wheat belt	1937, 1938	Durham <sup>8, 9</sup>	Alternaria, Hormodendrum
Coastal areas of Texas	1937	Prince and Morrow <sup>22</sup>	Monilia, Penicillium, Aspergillus, Trichoderma, Helminthosporium, Hormodendrum, Cladosporium
New England	1938	Pratt <sup>21</sup>	Alternaria, Hormodendrum, Aspergillus, Penicillium, Chaetomium
Pacific Northwest	1938	Schonwald <sup>26</sup>	Alternaria, Aspergillus, Hormodendrum, Trichoderma, Mucor, Rhizopus
Ann Arbor, Mich.	1939	Biggs and Sheldon <sup>3</sup>	Alternaria, Hormodendrum, Penicillium
Cincinnati	1939	King <sup>17</sup>	Alternaria
Iowa	1939	Halpin <sup>14</sup>	Alternaria, Hormodendrum
Seattle and vicinity	1940	Stroh <sup>27</sup>	Hormodendrum, Alternaria, Aspergillus, Cephalosporium, Cladosporium, Monilia, Mucor, Penicillium, Rhizopus
Nashville, Tenn	1940	Pennington <sup>20</sup>	Alternaria, Hormodendrum, Penicillium, Aspergillus, Mucor, Rhizopus
Missouri	1940	Hansel <sup>15</sup>	Alternaria, Hormodendrum, Helminthosporium
Detroit, Mich.	1941	Waldbott, Blair and Ackley <sup>29</sup>	Penicillium, Alternaria, Monilia, Aspergillus, Hormodendrum
Louisville, Ky.	1942	Vander Veer et al. <sup>28</sup>	Alternaria, Hormodendrum
Buffalo, N. Y.	1942	Cohen <sup>7</sup>	Hormodendrum, Alternaria, Penicillium, Mucor, Aspergillus
Chicago, Ill.	1942	Bernstein and Feinberg <sup>3</sup>	Alternaria, Hormodendrum
Central and South-western Parts of U. S.	1942	Morrow, Lowe and Prince <sup>18</sup>	Alternaria, Hormodendrum
San Diego, Cal.	1945	Harsh and Allen <sup>16</sup>	Hormodendrum, Alternaria, Penicillium, Macrosporium, Helminthosporium
San Antonio, Texas	1946	Bieberdorf <sup>4</sup>	Hormodendrum, Alternaria, Helminthosporium, Spondyloendium, Fusarium, Aspergillus, Penicillium

those from outdoor air. The percentages of these molds in indoor air indicate that indoor air contains a mixture of the molds from outdoor air and of those from house dusts. Although *Phycomyces*, *Mucor*, and *Rhizopus*, the only *Phycomycetes* found, comprised 6.0 per cent, 1.7 per cent, and 3.2 per cent, respectively, of the molds in house dusts, these genera

were not encountered in either outdoor air or indoor air, except *Phycomyces*, which was found only to the extent of 0.7 per cent of the molds in indoor air. While *Macrosporium* and *Monotospora* were isolated only from out-

TABLE IV. MOLD GENERA REPORTED IN SURVEYS, OF AIR-BORNE MOLDS

Mold genus	Number Investigators Reporting	Kentucky Survey
<i>Alternaria</i>	21	+
<i>Penicillium</i>	18	++
<i>Aspergillus</i>	17	++
<i>Hormodendrum</i>	17	++
<i>Mucor</i>	7	+
<i>Helminthosporium</i>	6	—
<i>Cladosporium</i>	5	—
<i>Monilia</i>	5	—
<i>Rhizopus</i>	5	+
<i>Trichoderma</i>	4	—
<i>Macrosporium</i>	3	+
<i>Fusarium</i>	2	—
<i>Cephalosporium</i>	1	+
<i>Ghaetomium</i>	1	—
<i>Monosporium</i>	1	—
<i>Oospora</i>	1	+
<i>Spondylocadium</i>	1	+
<i>Tilachlidium</i>	1	+
<i>Monotospora</i>	0	++
<i>Phycomyces</i>	0	++
<i>Stemphylium</i>	0	++
<i>Tetracoeosporium</i>	0	+

TABLE V. DISTRIBUTION OF MOLDS IN OUTDOOR AIR, INDOOR AIR, AND HOUSE DUSTS  
Condensed from Table I and Table II.

Molds	Outdoor Air %	Indoor Air %	House Dusts %
Fungi Imperfecti:			
<i>Alternaria</i>	17.8	10.6	1.5
<i>Aspergillus</i>	1.3	17.5	23.9
<i>Cephalosporium</i>	1.0	2.9	0.2
<i>Hormodendrum</i>	15.5	14.2	12.8
<i>Macrosporium</i>	0.7	0.0	0.0
<i>Monotospora</i>	1.6	0.0	0.0
<i>Oospora</i>	3.9	1.0	1.7
<i>Penicillium</i>	55.3	52.4	47.9
<i>Stemphylium</i>	0.7	0.0	0.0
<i>Tetracoeosporium</i>	0.0	0.0	0.4
<i>Tilachlidium</i>	2.2	0.7	0.7
Phycomyces:			
<i>Mucor</i>	0.0	0.0	1.7
<i>Phycomyces</i>	0.0	0.7	6.0
<i>Rhizopus</i>	0.0	0.0	3.2
Totals	100.0	100.0	100.0

door air, and *Tetracoeosporium* was isolated only from house dusts, the percentage of each was too small to be of significance. *Penicillium*, *Hormodendrum*, and some of the molds that were found in small numbers were evenly distributed in outdoor air, indoor air, and house dusts.

Referring again to Tables I and II, it may be seen that certain species also were found to predominate in outdoor air, others in indoor air, and still others in house dusts. *Aspergillus luchuensis* was isolated almost entirely from house dusts, although the genus *Aspergillus* as a whole was

found almost as frequently in indoor air as in house dusts. Although the genus *Hormodendrum*, as a whole, appeared to be evenly distributed in the three sources, *Hormodendrum cladosporioides* was isolated almost entirely from house dusts, *Hormodendrum nigrescens* almost entirely from indoor air, and *Hormodendrum viride* almost entirely from outdoor air.

Perhaps the most significant finding of our survey is that certain molds occur predominantly in outdoor air and others in house dusts. It points to the possible importance of including house dust, as well as air, in surveys of mold distribution. This investigation is being continued.

#### SUMMARY AND CONCLUSIONS

A survey of mold distribution in outdoor air, indoor air and house dust in eastern Kentucky and in central and western Kentucky has been made.

Aside from *Penicillium* and *Phycomyces*, which were more prevalent in January, all the molds encountered in both months were more prevalent in March than in January. All the genera that were found in January were also found in March. In addition, eleven genera which were not found in January were found in March.

There was not much difference in the lists of mold genera encountered in the two regions of the state, except that *Monotospora* was encountered only in the central and western region while *Tetracoccusporium*, *Macrosporium* and *Stemphylium* were encountered only in the eastern region.

*Penicillium* was the most prevalent mold in both regions.

Of the genera reported in other parts of the country we failed to find *Monilia*, *Trichoderma*, *Helminthosporium*, *Cladosporium*, *Monosporium*, *Fusarium*, *Chaetomium* and *Spondyloradium*.

We found four genera, *Monotospora*, *Stemphylium*, *Tetracoccusporium* and *Phycomyces*, that had not been previously reported.

Our finding that certain molds occur predominantly in outdoor air, and others in house dusts, points to the possible importance of including house dust, as well as air, in surveys of mold distribution.

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# BACTERIOLOGICAL STUDIES OF MULTIPLE SCLEROSIS

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THE clinical diagnosis of the patients in this study was made by attending physicians and by consulting neurologists. The patients studied represented samplings of the disease from widely separated regions and widely different climates. The clinical history and physical examination gave no clue as to the probable cause of the disease, and its progressive course was similar regardless of place of residence, climate, occupation or nationality. The isolation, from infection foci in persons suffering from multiple sclerosis, of streptococci having elective affinity for the nervous system of animals and neurotropic cataphoretic velocity has been reported.<sup>9,10</sup> Evidence for the possible etiologic relationship of alpha streptococci isolated chiefly from nasopharynx, tonsils and teeth was sought by appropriate inoculation of animals, by agglutination and precipitation tests with the serums from persons afflicted, with antistreptococcic serum prepared in horses,<sup>11</sup> and with thermal antibody prepared *in vitro* from the streptococcus in NaCl solution suspensions by prolonged heating in the autoclave,<sup>12</sup> and with much less heat plus hydrogen peroxide.<sup>14</sup> In addition, presumptive tests were made for specific streptococcal antigen and antibody in skin or blood by intracutaneous injection of natural and thermal antibody and of streptococcal antigen, respectively.<sup>15</sup>

## METHODS OF STUDY

Pus or other exudate was expressed and scooped from infected tonsils with a small-sized laryngeal mirror bent to an angle of 35°. Pus was aspirated from the depths of pyorrhea pockets with a capillary pipette. Pulpless teeth were drawn in a sterile manner and the apical end was immediately severed with a bone-cutting forceps. The nasopharynx was swabbed without touching the tongue, with aluminum wire cotton-wrapped swabs bent to a suitable angle to obtain material from up and behind the soft palate. The exudates from sinuses in persons having sinusitis, from cervix uteri in women suffering from endocervicitis, from the prostate in men having prostatitis and from the stool in special instances were obtained by suitable means.

The several materials thus obtained were suspended routinely in 2 ml. of 0.2 per cent gelatine in Locke's solution, for microscopic examination of Gram-saffranine stained films, for inoculation of animals and for cultures. The type and dosage for direct inoculation of animals and for cultures was modified as indicated by the kind and number of bacteria found in stained films. As a rule, two rabbits were inoculated intracerebrally far forward in the right frontal lobe, one with 0.1 ml., the other with 0.2 ml.

of the suspension in 2 ml. of gelatine-Locke's solution of the washings of nasopharyngeal swabbing, of washing of the apices of pulpless teeth, and of pus from pyorrhea pockets and tonsils. Cultures of these were made on blood agar and in dextrose brain broth. The latter afforded a gradient of oxygen tension and other conditions which were found essential for the growth and isolation of specific types of alpha streptococci.

The dextrose brain broth was either freshly prepared or was boiled to drive off oxygen and cooled immediately before being inoculated. Seven ml. of blood were drawn into vacuum tubes, allowed to clot, centrifuged, the serum poured off, the clot partially mascerated and planted into dextrose brain broth. Cultures in this medium were also made of the freshly drawn spinal fluid. The dextrose brain broth was prepared by adding pieces of fresh or frozen calf or young beef brain to tall columns, 9 to 10 cm. in test tubes of 0.2 per cent dextrose broth adjusted to pH 7.2, in a proportion of approximately one part by volume of brain substance to seven parts of the dextrose broth, before autoclaving at 17 pounds pressure for thirty minutes. All cultures were incubated at 33° to 35° C.

Early in these studies, animals were inoculated with the primary cultures from the one tube of dextrose brain broth which had been inoculated, provided stained films revealed a pure culture of the streptococcus. Blood agar plates were made at the same time to determine the purity and type of streptococcus. If other organisms had also grown in the dextrose brain broth, blood agar plates were made, and the subculture in dextrose brain broth from one or more colonies of the streptococcus which grew on the blood agar plate was injected into animals. More recently it was found that specifically virulent streptococci grew in far higher serial dilutions in dextrose brain broth than saprophytic variants and other bacteria often also present in the material studied. Serial dilutions were made in dextrose brain broth, at steps of 1-100 or 1-10,000 in four to six or more tubes, each containing 15 ml. of this medium. Serial dilutions at 1-100 were made by transferring and thoroughly mixing 0.15 ml. with the same 1. ml. pipette from tube to tube, and dilutions at 1-10,000 were made with a nichrome wire which was not sterilized after the first transfer and to which there adhered approximately 1.5 cubic millimeters of the culture. Pure cultures of the streptococcus for inoculation of animals and other studies were obtained from the end point of growth. Rabbits and guinea pigs were routinely inoculated intracerebrally with 0.1 or 0.2 ml. of a 1-200 or 1-10,000 dilution in NaCl solution, and mice with 0.03 ml. of the dextrose brain broth culture, and with these amounts, respectively, of 1-10,000 dilution of pure cultures in the autoclaved chick embryo medium.<sup>13</sup> Pure cultures of the streptococcus thus isolated in dextrose brain broth from the several materials from persons and from the brain or blood of inoculated animals were grown for one culture generation in varying amounts of 0.2 per cent dextrose broth. These cultures were centrifuged, the supernatant liquid was discarded, and the streptococci were placed in

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dense suspensions of glycerol, two parts, and saturated NaCl solution, one part. These dense suspensions were made to contain the growth of from 150 to 500 ml. of the culture or approximately 300,000,000,000 to 1,000,000,000,000 organisms per ml. The suspensions containing the freshly isolated streptococci were kept in the refrigerator, and appropriate dilutions were made for precipitation and agglutination tests, for immunization of horses and for the preparation of vaccines and thermal antibodies. Agglutination tests were made at twofold dilutions of 1-20 to 1-160 or fivefold dilution of 1-10 to 1-1,250 of the serum from patients, and at fivefold dilutions of 1-20 to 1-2,500 of antistreptococcal serums and thermal antibody, in saline containing 0.2 per cent phenol, against suspensions in saline containing 0.2 per cent phenol and approximately 3,000,000,000 streptococci per ml. in the final dilution. The mixtures were incubated at from 48° to 50°C. for eighteen to twenty-four hours when readings were made. The degree of agglutination in each of the four dilutions was recorded according to the scale of 0 to 4 plus. A 4-plus agglutination in each dilution, or 16, would represent 100 per cent; a total of 6-plus, or 6/16 equalled 37.5 per cent of the total possible agglutination. The brain of animals and pieces of the medulla and spinal cord were fixed in 10 per cent formalin. Sections were stained with hematoxylin and eosin, by the Weigert method for myelin, and by a modified Gram-Weigert stain for bacteria, in which decolorization was carried to a fair blue instead of to the end point, and no counter stain was used.

### RESULTS

Cultures from the blood and spinal fluid in dextrose brain broth proved negative except in a few instances in which alpha type of streptococci were isolated. Intracerebral injections of the spinal fluid in animals were without effect. Cultures from material obtained from nasopharynx, tonsils and infected teeth uniformly yielded streptococci of the viridans or alpha type, in great preponderance or in pure culture, and only occasionally small numbers of beta hemolytic streptococci. Staphylococci and micrococcus catarrhalis often grew in varying numbers on the primary blood agar plate, and *H. influenzae* almost never.

A careful search for associated infections was made in thirty-two cases. A history of repeated attacks of tonsillitis was obtained in seventeen, of an antecedent attack of influenza in thirteen. Clearly infected tonsils or tonsillar tags were found in nineteen, pyorrhea in twenty-four, and one or more pulpless teeth in twenty-eight.<sup>17</sup> In no instance did the disease begin following removal of foci of infection nor could relapses be traced to the removal. Since the methods and period of time covered in studies of multiple sclerosis were similar to those made of other diseases of the nervous system, and to afford a ready means of comparing the results obtained, a summary of the results in these and in normal controls is included.

The mortality, incidence of symptoms, and isolations of the streptococcus



TABLE I. MORTALITY AND SYMPTOMS IN RABBITS FOLLOWING INTRACEREBRAL INOCULATION OF STREPTOCOCCI ISOLATED IN STUDIES OF MULTIPLE SCLEROSIS AND OTHER DISEASES OF THE NERVOUS SYSTEM AND ISOLATION OF STREPTOCOCCI FROM THE BRAIN OF INOCULATED ANIMALS

Groups and Inocula. Streptococci from Nasopharynx, Tonsils, Sinuses or Infected Teeth	Cases	Rabbits		Incidence of Symptoms (per cent)							Cultures from	
		Inoculated	Per Cent That Died	Hypersensitivity	Tremors	Spasms	Convulsions	Ataxia	Nystagmus	Paralysis	Brain	Per Cent Yielding Streptococci
Multiple Sclerosis	18	46	65	46	72	24	1	74	26	50	40	62
	21	42	52	29	74	21	0	52	35	42	34	65
Multiple Sclerosis	19	31	62	35	65	24	1	74	22	50	30	60
	61	122	60	36	70*	23	2	66	29	49	104	63
Spasmodic Torticollis	8	70	69	6	40	21	0	59**	11	22	58	67
	28	176	70	23	40	66***	0	59	19	22	130	89
Epileptic	50	60	60	25	58	55	15	40	10	13	41	80
	68	145	46	26	33	35	2	23	2	70	62	91
Idiopathic Epilepsy	46	106	71	25	75	75	34	13	5	16	72	93
	45	77	87	87	79	21	3	10	0	9	54	83
Normal Controls	77	106	23	2	4	2	0	10	7	8	97	25

\*Usually of severe "intension" type.  
\*\*Accompanied by tic-like and spasmodic movements of the head.  
\*\*\*Especially of the diaphragm.

from the brain of rabbits that were inoculated directly with saline suspensions or with cultures of the streptococcus on isolation and after animal passage, from altogether sixty-one persons suffering from multiple sclerosis, and in contrast the result in rabbits similarly inoculated with streptococci from spasmodic torticollis, persistent epidemic hiccup, encephalitis, poliomyelitis, epilepsy and schizophrenia and normal controls, are summarized in Table I. The mortality and isolations of streptococci from brain of inoculated rabbits and the incidence of symptoms referable to the nervous system were consistently much higher following inoculations of streptococci from persons suffering from multiple sclerosis and the other diseases of the nervous system than in those receiving the streptococcus from normal controls. The incidence and type of symptoms referable to the nervous system in the three groups of rabbits receiving streptococci isolated in studies of multiple sclerosis were strikingly similar to those at hand in persons suffering from this disease. The mortality and incidence of isolations of the streptococcus from brain of mice and guinea pigs receiving the streptococcus from multiple sclerosis were similar to those obtained in rabbits. Lesions of lungs in mice inoculated intraperitoneally were abnormally high, occurring in ten of eighteen mice so inoculated. Of 117 mice inoculated intracerebrally with forty strains of the streptococcus, seventy-three (62 per cent) died. Severe tremors were observed in forty-five, spasms in twenty-eight, ataxia in ten, paralysis in twenty-three and incontinence of urine in six. The streptococcus was isolated from the brain in thirty-four of the thirty-eight cultured. Of sixty-eight guinea pigs inoculated intracerebrally with twenty-six strains, thirty-six (53 per cent) died. Severe tremors developed in thirty-one, spasms in eighteen, ataxia in ten, paralysis in twenty-five, incontinence of urine in four and salivation with wet fur under chin in five. The streptococcus was isolated from the brain in twenty-seven of the twenty-nine cultured.

The incidence and type of symptoms in animals receiving the streptococcus isolated in studies of the other diseases of the nervous system were likewise similar in important respects to those more or less characteristic of the diseases in question. The statistical evidence of specificity, though often striking, does not adequately represent the results. Blurred vision or blindness, hyperactive reflexes and incontinence of urine, which developed not uncommonly in animals following inoculation of streptococci isolated in studies of multiple sclerosis, were not obtained or were obtained less often following inoculation of streptococci isolated in studies of the other diseases, and never following inoculation of the streptococcus from normal controls. Paralysis in the multiple sclerosis group of animals was relatively mild, usually spastic in type and was often associated with localized spasms. Ataxia, accompanied by tic-like and spasmodic movements of the head, was the characteristic picture in animals following inoculation of the streptococcus isolated in studies of spasmodic torticollis. Ataxia spasms of the diaphragm and abdominal muscles, sometimes associated with audi-

ble hiccup and hemorrhages in the diaphragm, characterized the findings in animals inoculated with the streptococcus isolated in studies of epidemic and postoperative hiccup. A wide range of symptoms developed in rabbits receiving the streptococcus isolated in studies of encephalitis, which corresponded to the wide range of symptoms at hand in the patients from whom the streptococcus inoculated was obtained. Muscular spasms and lethargy occurred in high incidence in animals receiving the streptococcus isolated, respectively, from persons having myoclonic and lethargic types of encephalitis. Flaccid paralysis with diminution or loss of knee jerks occurred in highest incidence in the poliomyelitis group of animals, and tremors, spasms, and ataxia were slight or absent. Moreover, nystagmus and incontinence of urine almost never occurred. The presence of specific types of streptococci in epidemic encephalitis and poliomyelitis is obviously not to be considered as the sole cause of these diseases independently of the viruses. Severe tremors and spasms, often associated with generalized convulsions resembling grand mal, occurred in highest incidence in the group of animals receiving the streptococcus from persons suffering from idiopathic epilepsy.<sup>16</sup> Extreme hyperirritability and tremors occurred in highest incidence in the group of animals receiving the streptococcus isolated in studies of schizophrenia. Catatonic states and strange changes in behavior often also developed in these, and virtually never occurred in the other groups of animals.<sup>16</sup>

Sterile filtrates of NaCl solution suspensions of material obtained directly from nasopharynx, tonsils and teeth, and of the dextrose brain broth cultures from persons having multiple sclerosis, when injected intracerebrally, caused transient tremors, in-co-ordination, congestion of eyes, and other mild symptoms soon after injection, followed by recovery. Late symptoms or deaths, indicating the possible presence of a virus, did not occur.

Streptococci isolated from the cervix uteri, from prostate and from the stool were without neurotropic virulence. The invasiveness or general virulence of the streptococcus isolated in studies of multiple sclerosis, in accord with the nature of the disease, was found to be of a low order. Inoculated animals did not die of a streptococcemia. Cultures were made of the blood of ninety-two rabbits that died after intracerebral inoculation of the streptococcus. The cultures remained sterile in seventy-three, and in only nineteen was the streptococcus obtained. Of the nineteen rabbits, the streptococcus was isolated in nine of twelve that died in twenty-four hours after inoculation; in six of nineteen that died on the second day; in three of thirteen that died on the third day; in one of eight that died on the fourth day, and in none of forty that died on the fifth to the sixtieth day.

As shown in Table I, cultures were made from the brain in 104 of the 122 rabbits that had been inoculated with material containing the streptococcus. Sixty-five (63 per cent) yielded the streptococcus. While the cultures in thirty-nine proved sterile, most of the thirty-nine died late from

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the effects of the inoculation, and a few were anesthetized while having active symptoms. Cultures from the blood of all of these remained sterile, and the streptococcus was not demonstrable in the lesions. The late symptoms and deaths were clearly due to causes other than an overwhelming infection. The probable presence of a streptococcal neurotoxin having predilection for vital nerve centers, or to which the vital centers had become allergic, was considered. Accordingly, emulsions of the brain and filtrates of emulsions were made from rabbits that died late, and whose blood and brain proved sterile, and from normal rabbits. These were inoculated intracerebrally into normal rabbits. All of six rabbits receiving emulsions and four receiving filtrates died—three on the day after inoculation, two in three days, two in four days, one in seven, and two in fourteen days. The material inoculated and cultures from the brain of all that died proved sterile. None of these rabbits developed symptoms suggestive of multiple sclerosis. The emulsions of the brain and filtrates of emulsions from normal rabbits similarly inoculated proved innocuous.

### 5 ILLUSTRATIVE EXPERIMENTS IN ANIMALS AND PROTOCOLS

A mixture of equal parts of the cultures of the streptococcus isolated from the nasopharynx of sixteen persons suffering from multiple sclerosis, and grown separately in chick embryo medium for from seven to forty-two days, was made, and a 1-10,000 dilution was inoculated intracerebrally in eight rabbits, twelve guinea pigs and one monkey. Intension tremors developed in seven of the eight rabbits and in eight of the twelve guinea pigs, ataxia in six and five, respectively, exaggerated knee jerks in eight and seven, nystagmus in six and two, ataxia in six and two, localized paralysis in seven and eight, spasms of muscles in five and six, incontinence of urine in four and three, and drooling of saliva in two and four. Blurred vision developed in three, and blindness in two, of the eight rabbits. Seven of the rabbits and seven of the guinea pigs died in from two to twelve days following inoculation. The rest were anesthetized. The streptococcus was isolated from the brain in dextrose brain broth in all of the twelve guinea pigs and in the rabbits that died within six days, and in only one of the rest. The details of experiments and results obtained in this series of rabbits, guinea pigs and the monkey, and in other rabbits, are depicted in Protocols 1, 2, 3, and 4.

*Protocol 1.*—A white rabbit weighing 1,800 grams was injected intracerebrally on June 11, 1943, with 0.1 ml. of sterile chick embryo medium to lower the inherently high resistance of the brain to infection, and 2 ml. of the undiluted culture from nasopharynx was injected into the tongue. The animal was well June 12. On June 13, moderate tremors of masseters and muscles of the neck and tremors of extremities on exertion were noted. On June 14, weakness of the left fore extremity, severe tremors and twitchings of the muscles of the neck, exaggerated reflexes and ataxia had developed. The paralysis and tremors were worse on June 15, and the animal was found dead on June 16. Moderate hemorrhagic edema of lungs and congestion of

TABLE II. AGGLUTININATIVE TITER OF THE SERUM OF PERSONS SUFFERING FROM MULTIPLE SCLEROSIS, MIGRAINE, SCHIZOPHRENIA AND ARTHRITIS FOR STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE DISEASES

Serum from Persons Suffering from:	Number of Serums	Average Cutaneous Reaction Indicating Antibody	Percentage of Agglutination by Serum of Patients at Twofold Dilutions of 1-20 to 1-160 of:									
			Streptococci isolated in studies of:									
			Multiple sclerosis, stages					Quiescent				
			Active									
			8163	3248	2405	3706	3749	3027	3238	Migraine	Schizo- phrenia	Arthritis
Multiple Sclerosis	6	High (10.67 sq. cm.)	32	59	35	72	69	0	0	19	12	4
	7	Moderate (4.91 sq. cm.)	29	55	28	76	58	0	0	13	2	1
	7	Low (1.65 sq. cm.)	24	49	21	58	44	0	0	18	9	0
Migraine Schizophrenia Arthritis	7	6.28 sq. cm.	4	22	13	32	27	0	0	51	13	4
	6	4.91 sq. cm.	0	17	8	33	19	0	0	17	30	0
	3	7.85 sq. cm.	2	19	5	33	20	0	0	4	4	35

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the brain were found. Cultures in dextrose brain broth from the brain and blood yielded a pure culture of the streptococcus.

*Protocol 2.*—A medium-sized white rabbit was inoculated intracerebrally on June 1, 1943, with 0.1 ml. of a 1-10,000 dilution in 0.2 per cent dextrose brain agar of a serial dilution culture of the streptococcus which grew in dextrose brain broth at 10<sup>-8</sup> dilution of the NaCl solution washings of the nasopharyngeal swabbing. On June 2 the animal seemed well when quiet in its cage, but on exertion, tremors of extremities developed. On June 3, extreme intension tremors, ataxia, exaggerated knee reflexes and weakness of adductors of fore extremities were noted. From June 3 to 8, the animal remained about the same. On June 9 it seemed well when quiet in cage, but on exertion, severe tremors, ataxia, blurred vision, horizontal nystagmus and tilting of head to the right were noted. On June 10 it was about the same. On June 11 and 12, the symptoms were worse, and the animal was found dead on June 13. There was no mark at the point of intracerebral injection. The meninges were normal. The brain was moderately congested. The optic nerves were congested and edematous. There were no lesions of the viscera. Dextrose brain broth cultures from the brain yielded a pure culture of the streptococcus.

*Protocol 3.*—A guinea pig weighing 350 grams was inoculated intracerebrally on June 11, 1943, with 0.01 ml. of a 1-10,000 dilution of the chick embryo cultures of the streptococcus. On June 12 and 13, there were no apparent symptoms. On June 14 severe tremors on exertion and moderate spastic paralysis of hind extremities were noted. On June 16 spastic gait, ataxia, severe intension tremors, nystagmus and wetting of the fur under the chin were present. On June 17 the symptoms were about the same. On June 19 intension tremors were extreme, often bordering on generalized spasms, associated with severe ataxia and spastic weakness of hind extremities. It was anesthetized to death. Fur under the chin was wet due to drooling of saliva. Aside from moderate congestion of the brain, no lesions were found. Dextrose brain broth cultures from the brain yielded a pure culture of the streptococcus.

*Protocol 4.*—A medium-sized rhesus monkey was inoculated intracerebrally on June 1, 1943, with 2 ml. of a 1-10,000 dilution in .2 per cent dextrose brain agar of the primary dextrose brain broth culture of the streptococcus from the nasopharyngeal swabbing of a person in the active stage of multiple sclerosis. The monkey was apparently well on June 2. On June 3 it seemed well when undisturbed in its cage, but when it jumped from its cage, undoubted weakness of hind extremities was noted. On June 4, severe tremors on exertion, horizontal nystagmus and incontinence of urine had developed. The temperature was normal. These symptoms disappeared, and on June 11 it was inoculated intracerebrally with 1 ml. of a 1-10,000 dilution of the mixtures of the chick embryo cultures of the streptococci from the sixteen persons having active symptoms of multiple sclerosis, and intralingually with 2 ml. of the undiluted mixture of cultures. On June 12 at 9:00 a.m., the animal refused to leave its cage, and when made to do so, severe tremors and undoubted weakness of hind extremities and incontinence of urine became manifest, and exaggerated knee jerks were elicited. On June 13 it sat quietly in its cage, apparently blind. On exertion, severe tremors, bordering on mild generalized spasms, ataxia, and spastic weakness of extremities were noted. It bumped into the walls of its cage as it moved aimlessly about. The pupils were widely dilated and did not respond to light. Severe and continuous horizontal nystagmus had developed. On June 14 it was found dead. Necropsy revealed congestion of the brain, infiltration and edema surrounding the optic nerve and chiasm, and also of spinal nerves and the anterior aspect of the medulla. A small cyst was found at the point of injection in the

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TABLE III. AGGLUTINATION OF STREPTOCOCCI ISOLATED IN STUDIES OF MULTIPLE SCLEROSIS AND OTHER DISEASES BY THE SERUMS OF PERSONS HAVING MULTIPLE SCLEROSIS AND THE SERUMS FROM PERSONS CONVALESCING FROM RESPIRATORY INFECTIONS

Pools of Streptococci Isolated in Studies of:	Number of Strains in Pools	Percentage of Total Possible Agglutination by the Serums at Fivefold Dilutions of:	
		1-10 to 1-1250 of persons:	
		Suffering from	Convalescent from
		Multiple Sclerosis. Average for Serums from 10 cases	Respiratory Infections. Average for Serums from 40 cases
Multiple Sclerosis	10	66	31
	7	72	33
Encephalitis	Many	33	20
Poliomyelitis		21	5
Respiratory Infection		12	53
Arthritis		13	9
Well Controls		19	13

TABLE IV. AGGLUTINATIVE TITER OF ANTISTREPTOCOCCIC SERUMS FOR CLOSELY RELATED, HOMOLOGOUS AND DISTANTLY RELATED STREPTOCOCCI

Source of Streptococci	Strains or Cases	Cultures	Percentage Incidence of Maximal and Indeterminate Agglutinations at Fivefold Dilutions of 1-20 to 1-2500 by Antiserums Prepared with Streptococcus Isolated in Studies of:						
			Encephalitis	Poliomyelitis	Influenza	Arthritis	Epilepsy	Schizophrenia	Indeterminate
Multiple Sclerosis	19	98	64	23	5	0	—	—	8
Encephalitis	10	12	58	0	0	0	17	25	0
Epilepsy	10	12	8	0	0	0	75	517	0
Schizophrenia	23	45	13	0	0	0	31	7	0
Arthritis	10	30	7	0	3	70	10	0	10
Normal Controls	71	71	15	4	17	7	12	7	38

right frontal lobe. The viscera were normal. Dextrose brain broth cultures of pipettings of cerebrospinal fluid admixed with brain substance revealed a pure culture of the streptococcus.

## RESULTS OF AGGLUTINATION AND PRECIPITATION TESTS

The results of agglutination tests made with the serums and streptococci from persons having multiple sclerosis, in contrast to those obtained in control studies, are summarized in Table II. It will be seen that the streptococci isolated in studies of multiple sclerosis, migraine, schizophrenia and arthritis were agglutinated in highest titer by the respective homologous serums. Moreover, the agglutinative titer of the serums and the antibody titer in skin or blood, as determined by the cutaneous tests, ran closely parallel. This was especially true in multiple sclerosis. The streptococci isolated during the quiescent stage of multiple sclerosis were not agglutinated by any of the serums.

The agglutinative titers of serums from persons having active multiple sclerosis, and, in contrast, of serums from persons convalescing from respiratory infections, for streptococci isolated in studies of persons having

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TABLE V. AGGLUTINATION OF STREPTOCOCCI BY THERMAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF MULTIPLE SCLEROSIS AND OTHER DISEASES

Thermal Antibody Prepared from Streptococci Isolated in Studies of:	Pools of Streptococci	Percentage of Total Possible Agglutination of Respective Streptococci at Fivefold Dilutions of from 1-20 to 1-2500 of Thermal Antibody Prepared from Streptococci Isolated in Studies of:							
		Multiple Sclerosis		Respiratory Infection	Schizophrēnia	Migraine	Arthritis	Controls	
		8463	3719	3738	2839	3750	3961	Pneumococci Types I, II, III	Staphylococcus
Multiple Sclerosis	8463	63	81	56	56	50	56	38	31
	3719	63	88	63	63	69	50	19	31
Respiratory Infection	3738	50	63	88	69	69	50	19	19
Schizophrēnia	2839	38	63	56	81	63	11	25	13
Migraine	3750	31	56	69	69	88	56	19	13
Arthritis	3961	13	11	56	50	11	69	19	19
Controls—									
Type Pneumococci I, II, III	3689	0	25	11	14	50	38	69	25
Staphylococci	8406	0	25	19	31	25	25	19	44
NaCl Solution		6	19	25	19	25	25	19	13

TABLE VI. PRECIPITATION AT THE INTERFACE BETWEEN THE SERUMS AND WASHINGS OF NASOPHARYNGEAL SWABBINGS OF PERSONS HAVING MULTIPLE SCLEROSIS AND ANTISERUMS PREPARED WITH STREPTOCOCCI ISOLATED IN STUDIES OF ENCEPHALITIS, POLIOMYELITIS AND RESPIRATORY INFECTIONS

Materials Used as Antigen	Cases	Percentage Incidence of Precipitation at the Interface with:					
		Antiserums Prepared in Horses with Streptococci Isolated in Studies of:				Anti-pneumococci Serums I, II, III	Normal Horse Serum
		Encephalitis	Poliomyelitis	Respiratory Infection	Arthritis		
Serums from Cases	5	80	60	20	0	0	0
	16	50	62	62	0	7	0
	11	55	36	55	18	0	0
NaCl Solution Washings from Nasopharyngeal Swabbings	Undiluted	17	76	82	0	0	0
	Diluted 1-10		41	29	0	0	0
	Undiluted	11	100	73	27	18	0

these and other diseases, are summarized in Table III. A high degree of respective specificity is shown.

The results of a long series of agglutinative tests with antiserums prepared in horses with streptococci isolated in studies of different diseases of the nervous system, of influenza and of arthritis, and the homologous, closely and distantly related streptococci, are summarized in Table IV. Agglutinative titers for homologous and closely related strains were consistently much higher than for more distantly related strains. Evidence indicating antigenic and other differences in alpha streptococci isolated in studies of multiple sclerosis, and of those isolated in studies of other dis-



TABLE VII. ERYTHEMATOUS REACTIONS FOLLOWING INTRADERMAL INJECTION OF "NATURAL"  
AND THERMAL ANTIBODY IN PERSONS HAVING MULTIPLE SCLEROSIS  
IN RELATION TO HISTAMINE INJECTIONS

Groups	Reactions to Intradermal Injection of:											
	Natural Antibody						Thermal Antibody					
	Prepared from Streptococci Isolated in Studies of:											
	Persons Tested	Polio-myelitis	Enceph-alitis	Arthritis	Respir-atory Infection	Pneumo-coccal Types I, II, III	Persons Tested	Polio-myelitis	Enceph-alitis	Arthritis	Multiple Sclerosis	Well Persons
Multiple Sclerosis	10	5.96	9.80	2.60	1.33	—	14	5.16	7.24	2.88	13.23	1.08
	13	6.11	8.38	2.12	—	1.42	12	2.96	6.24	2.88	13.57	
	9	7.64	11.48	2.42			15	1.78	6.61	2.82	18.46	0.93
Well Persons Remote from Epidemics	Many	1.27	0.79	1.48	2.23	—	Many	1.80	0.79	1.54	0.83	0.89
	Many	3.27	6.88	1.80	3.06	—	Many	14.21	9.23	2.21		
	Many	8.97	3.30	2.41	3.21		Many		4.21	2.45		3.09
	Many	4.10	7.38	3.12	5.12		Few		12.32	1.76		
	87	1.50	2.60	8.12			19		3.47	9.63		

eases, is strikingly shown in Table V. Comparable suspensions in NaCl solution of each of the different groups of strains, when autoclaved with hydrogen peroxide, yielded agglutinins in highest titer for the respective homologous strains.<sup>14</sup>

Results of precipitation reactions at the interface between the serums of horses that had been immunized with streptococci from encephalitis, poliomyelitis and respiratory infections closely related to streptococci from multiple sclerosis, and the serums and NaCl solution extracts of nasopharyngeal swabbings from persons having multiple sclerosis, are summarized in Table VI. A much higher incidence of precipitation occurred with the antisera from encephalitis, poliomyelitis and respiratory infections than with antisera prepared with the streptococci from arthritis, and than with anti-pneumococcal and normal horse serum.

The effects of intravenous injections of histamine on the specific streptococcal antigen content in skin or blood, determined by the intradermal injection of "natural" and artificial or thermal streptococcal antibody<sup>12</sup> in persons having multiple sclerosis, are summarized in Table VII. A significant diminution in antigen occurred, as measured by the intradermal injection of natural antibody prepared in horses with streptococci isolated in studies of encephalitis and poliomyelitis, and a striking specific drop occurred as measured with thermal antibody prepared *in vitro* from streptococci isolated in studies of multiple sclerosis.

The effects of intravenous injections of histamine on the cutaneous reactions to the specific thermal antibody and antigen in thirteen persons having multiple sclerosis are summarized in Table VIII. The reactions to antibody, indicating antigen, were uniformly far greater, and to antigen, indicating antibody in skin or blood, were uniformly far less, in the two persons before treatment with histamine and the seven other persons not receiving histamine (not included in the table) than the reactions indicating antigen and antibody, respectively, one-half to two hours after daily intravenous histamine injections. Moreover, reactions indicating antigen were significantly less in twelve of the thirteen persons receiving histamine, and reactions indicating antibody greater in eight, one-half to two hours after histamine, than the reactions twenty-four hours after histamine injections. The diminution in antigen and increase in antibody was by far the greatest after the first histamine treatment.

The effects on the cutaneous reactions to natural antibody, prepared with closely related streptococci from encephalitis and poliomyelitis, of treatment of persons having multiple sclerosis with histamine alone, and of treatment with histamine and specific thermal antibody, are summarized in Table IX. It will be seen that there was a far greater reduction in reactions indicating antigen following the combined treatment, than with histamine alone. This is in accord with the results obtained in a number of persons having multiple sclerosis treated with vaccine and thermal antibody prepared from streptococci isolated in studies of multiple

TABLE VIII. THE EFFECT OF HISTAMINE INJECTIONS IN PERSONS HAVING MULTIPLE SCLEROSIS ON THE SPECIFIC STREPTOCOCCAL ANTIGEN AND ANTIBODY TITER IN SKIN OR BLOOD AS DETERMINED BY THE REACTION FOLLOWING INTRACUTANEOUS INJECTION RESPECTIVELY OF THERMAL ANTIBODY AND OF ANTIGEN

No.	Age	Sex	Number of Histamine Treatments		Clinical Results	Cutaneous Reactions (sq. cm.) Indicating Streptococcal Antigen and Antibody Respectively in Skin or Blood Characteristic of:							
			Previous Series,	Present Series		Multiple Sclerosis		Arthritis		Multiple Sclerosis		Arthritis	
						Antigen	Antibody	Antigen	Antibody	Antigen	Antibody	Antigen	Antibody
3710	35	M	0	1	?	19.61*	1.77	4.91	3.14	12.57	3.14	12.57	3.14
3711	21	F	0	1	?	19.61*	1.77	3.14	7.07	12.57	1.77	12.57	1.77
3700	19	M	0	26	Improved	9.62	3.14	0	7.07	4.91	0	4.91	0
3701	33	M	0	22	Improved	9.62	12.57	0	3.14	9.62	0	9.62	0
3705	29	F	0	36	Improved	9.62	7.07	0	7.07	3.14	0	3.14	0
3717	46	F	0	40	Improved	4.91	9.62	0	3.14	12.57	0	12.57	0
3713	38	F	0	62*	Improved	3.14	7.07	4.91	4.91	4.91	0	4.91	0
3704	27	F	Many	59	Improved	12.57	7.07	3.14	3.14	9.62	0	9.62	0
3703	36	M	200	10	Markedly Improved	7.07	12.57	0	3.14	4.91	4.91	4.91	4.91
3712	18	F	Many	18	Markedly Improved	3.14	4.91	0	3.14	7.07	0	7.07	0
3714	32	F	382	45	Disease Quiescent	1.77	12.57	0	1.77	12.57	0	12.57	0
3716	51	F	39	46	Improved	4.91	9.62	4.91	3.14	12.57	0	12.57	0
3702	32	M	200	?	Improved	7.07	12.57	0	3.14	4.91	0	4.91	0
Total average						8.67	7.10	0.91	4.45	8.75			1.05

# MULTIPLE SCLEROSIS—ROSENOW

TABLE IX. THE EFFECT ON CUTANEOUS REACTIONS IN PERSONS HAVING MULTIPLE SCLEROSIS OF TREATMENT WITH HISTAMINE ALONE AND TREATMENT WITH HISTAMINE AND SPECIFIC THERMAL ANTIBODY

Groups		Cases	Erythematous Reactions to Intradermal Injection of Natural Antibody Prepared in Horses with Streptococci Isolated in Studies of:							
			Chronic Encephalitis		Acute Poliomyelitis		Arthritis		Pneumonia	
			Sq. cm.	Re- actions 5 sq. cm. or more. Per Cent	Sq. cm.	Re- actions 5 sq. cm. or more. Per Cent	Sq. cm.	Re- actions 5 sq. cm. or more. Per Cent	Sq. cm.	Re- actions 5 sq. cm. or more. Per Cent
Multiple Sclerosis	Before Treatment	9	10.34	78	5.84	56	2.54	11	0	0
	After from 8 to 45 Daily Treatments with Histamine	9	7.41	78	4.54	47	1.71	0	1.48	0
	After from 1 to 47 Daily Treatments with Histamine and from 1 to 10 Injections of Thermal Antibody*	7	2.11	0	2.21	0	0.81	0	0	0
Arthritis, untreated controls		8	1.45	0	1.18	0	4.74	63	1.06	0

\*Thermal antibody was injected subcutaneously every other or every third day. Each injection consisted of 1 ml. of a 1-10 dilution of the supernatant of NaCl solution suspension of 20,000,000,000 streptococci per ml. isolated in studies of multiple sclerosis after autoclaving for 96 hours.

sclerosis. These results were similar to those obtained in a man of middle age having advanced multiple sclerosis. The cutaneous reaction to antibody on January 3, 1947, before treatment, was 19.64 sq. cm., and to antigen, 0. On February 24 these reactions were 15.90 and 12.57, respectively; on May 21, 7.07 and 4.91, and on Nov. 11, 3.14 and 4.91. Coincident with the striking reduction of antigen and increase of antibody, the symptoms indicating activity disappeared.

## THE GROSS AND MICROSCOPIC LESIONS

Abscess formation in the brain at the site of injection of material containing the streptococcus and diffuse suppurative meningitis almost never occurred. Diffuse congestion of the brain, edema, and leukocytic infiltration over the anterior surface of the pons and medulla were common, especially in rabbits that died in from two to four days following inoculation of washings of nasopharyngeal swabbings and suspensions of pus from tonsils and pyorrhea pockets. This was less common following inoculation of highly diluted pure cultures of the streptococci. Severe congestion of the mucous membrane of the trachea, with or without hemorrhagic edema of the lungs, was found commonly in rabbits that succumbed soon after inoculation. The bladder was often greatly distended with urine in animals in which severe paralysis had developed.

The microscopic lesions were most numerous in the white matter of the cerebrum; pons, peduncles of cerebellum and the posterior and lateral col-



Fig. 1. Area of degeneration and round cell infiltration surrounded by partially occluded blood vessels, due to endovascular and perivascular infiltration by round cells in the lateral column of the spinal cord of a rabbit, seven days after intracerebral inoculation of the streptococcus. H. and E. stain  $\times 175$ .



Fig. 2. Perivascular and diffuse round cell infiltration in the wall of the lateral ventricle in the brain of a rabbit, seven days following intracerebral inoculation of the streptococcus. H. and E. stain  $\times 175$ .

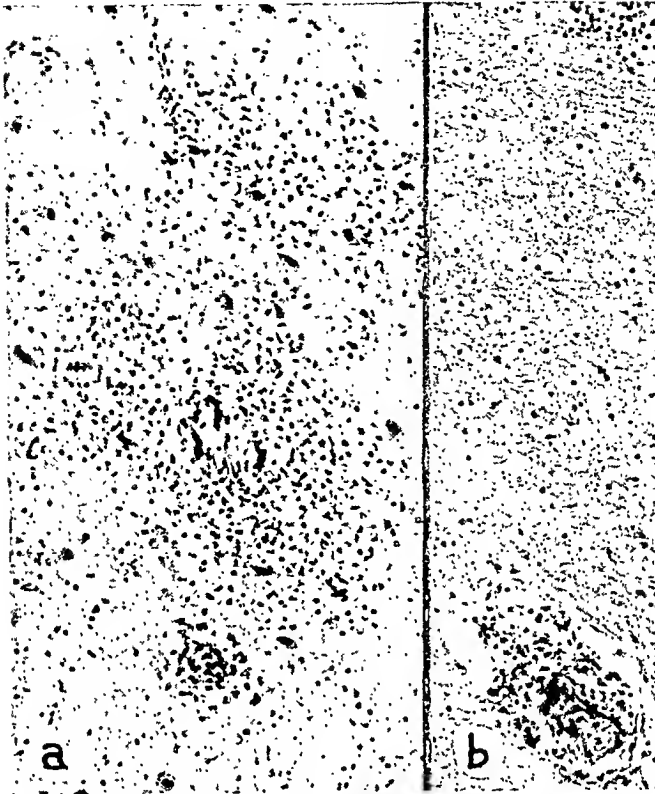


Fig. 3. (a) Endovascular, perivascular and diffuse round cell infiltration, degeneration and edema in the midbrain, and (b) perivascular infiltration, edema and degeneration in the cerebellum of a monkey, thirteen days following the first and two days following the second intracerebral inoculation of the streptococcus (Protocol 4). H. and E. stain  $\times 175$ .



Fig. 4. Medulla of the rabbit, referred to in Protocol 2, twelve days following intracerebral inoculation of a 1-10,000 dilution of dextrose brain broth culture of the streptococcus. Note the unstained extensive patchy disseminated areas of demyelination especially posteriorly. Weigert myelin stain  $\times 12$ .



Fig. 5. "Disseminated sclerosis—medulla. Several areas of demyelination are present in the section. These are unstained, well-defined and variable in size and shape."<sup>7</sup> The photomicrograph is of a person that died of multiple sclerosis. Weigert-Pal myelin stain  $\times 9$ .

umns of the spinal cord. Hemorrhages, edema, polymorphonuclear leukocytic infiltration, and degeneration, especially surrounding blood vessels, characterized the microscopic picture in animals that succumbed soon after inoculation. Degeneration and infiltration by lymphocytes and plasma cells predominated in the lesions of animals that died or were anesthetized long after inoculation. The lesions were often related to blood vessels which were partially or completely occluded by thrombi, or more often, by endovascular and perivascular proliferation of cells resembling lymphocytes, endothelial, and plasma cells (Figs. 1, 2 and 3). Occlusion of blood vessels by fibrinous clots of fibrin were not found.<sup>6</sup> Hemorrhage and edema were found in the wall and immediately surrounding fair-sized blood vessels in the pia and white matter of the medulla and in the posterior and lateral columns of the spinal cord. Regardless of these important lesions, the most striking parallelism between the experimentally produced and natural occurring lesions was the demyelination, as shown by the Weigert and Weigert-Pal special stains for myelin<sup>7</sup> (Figs. 4 and 5). The optic nerves



Fig 6 Edema and interstitial round cell infiltration of the optic nerve of the monkey in which blindness developed (Protocol 4). Note in addition the absence of lesions within the eye and the great swelling of the optic nerve immediately outside of the incisive sclera of the eyeball. H and E stain  $\times 25$ .

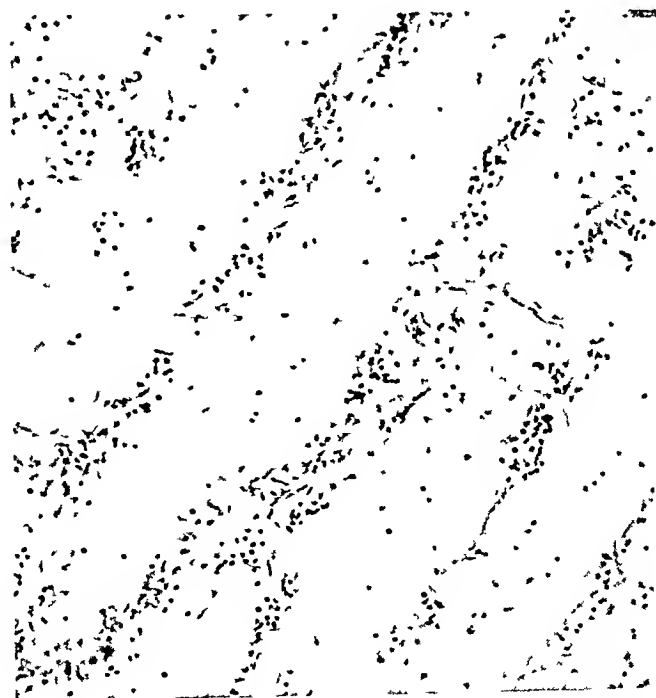


Fig 7 Interstitial edema and round cell infiltration of the optic nerve shown in Fig 6. H and E stain  $\times 175$ .



## MULTIPLE SCLEROSIS—ROSENOW

of the monkey that became blind were edematous and swollen (Fig. 6). In some instances, the posterior roots of the spinal nerves were found edematous and infiltrated, but in no instance were lesions found in the inter-

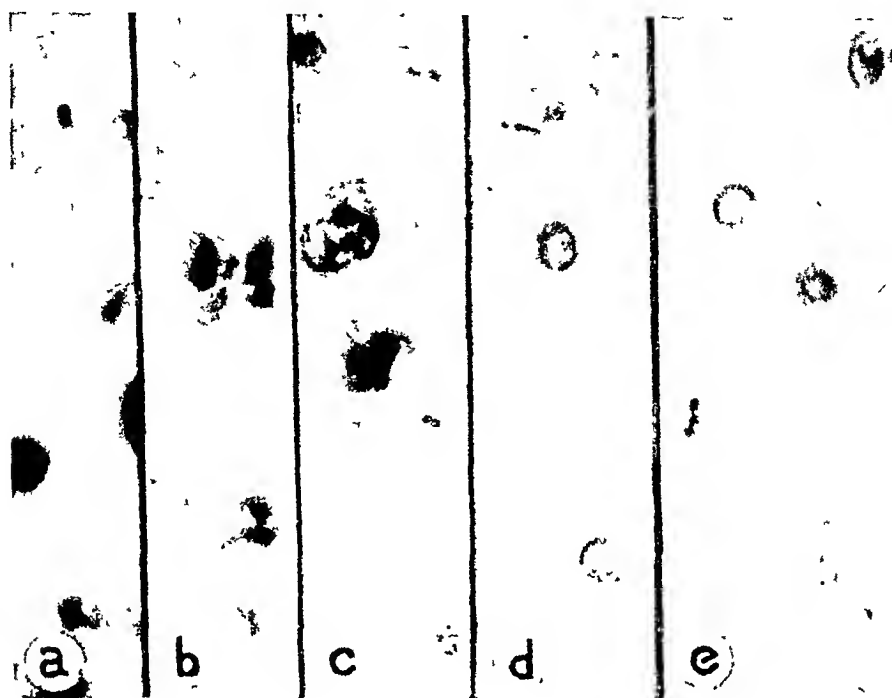


Fig. 8. Diplococci or streptococci in perivascular and other areas of edema and cellular infiltration in rabbits (a and b), and in the monkey referred to in Protocol 4: (c) in the brain, (d) in the cerebellum and (e) in the optic nerve. Modified Gram stain  $\times 1400$ .

vertebral ganglia. The anterior columns of the spinal cord and gray matter of the brain were conspicuously free from lesions.

Sections stained for bacteria revealed large or small numbers of diplococci, singly and in short chains in the lesions depending on the duration of the experiment (Fig. 8, a, b, c and d). Organisms were not demonstrable in the lesions after cultures from the brain proved sterile. Edema, infiltration by polymorphonuclear leukocytes, lymphocytes and plasma cells (Fig. 7), and the streptococcus were demonstrated microscopically in the edematous areas in the sheath and between the fibers of the optic nerve in rabbits and the monkey that had developed blurred vision or blindness (Fig. 8, e). No lesions were found within the eyes in such animals (Fig. 6).

### SUMMARY AND COMMENTS

The results of a bacteriologic study of multiple sclerosis made by special methods is reported, and the mechanism by which an infective agent may cause a disease in which the usual manifestations of an infectious etiology are largely lacking is discussed. A green-producing or alpha type of streptococcus was consistently isolated from nasopharynx, tonsils and infected

The cardinal symptoms of this disease were reproduced or closely simulated on appropriate intracerebral inoculation in mice, guinea pigs, rabbits and monkeys with saline suspensions of the streptococcus obtained directly from the patient, with pure cultures of the freshly isolated strains, with strains after twenty or more rapidly repeated subcultures in dextrose brain broth, and with strains after one or more passages through animals. The "spotty" distribution of the lesions in the white matter of the brain and cord, hemorrhage, edema, demyelination and infiltration by round cells immediately surrounding blood vessels, and other lesions in relation to vascular beds, and their similarity to the early lesions of multiple sclerosis, have been reproduced or simulated.<sup>1</sup> Partial or complete occlusion of vessels by thrombosis, endovascular and perivascular proliferation of, or infiltration by, lymphocytes and other cells, occurred in these experiments quite as these occur in relation to the lesions of multiple sclerosis.<sup>2,8</sup> and the lesions of other diseases of the nervous system.<sup>18</sup>

Lesions of the lungs in rabbits and mice developed not infrequently following inoculation of the streptococcus, which is in accord with the fact that the onset of the disease and especially exacerbations or extensions often follow attacks of influenza or other respiratory infections.<sup>3,17</sup>

The different strains isolated during the active stage of the disease were agglutinated specifically by the serums of persons stricken, by antisera prepared with closely related streptococci, such as those from encephalitis, and by thermal antibody prepared *in vitro* from streptococci isolated in studies of multiple sclerosis.

Specific streptococcal antigen was demonstrated in skin or blood of persons in the active stage of the disease by intradermal injection of solutions of the respective closely related "natural" and specific streptococcal thermal antibodies, and specific streptococcal antibody was demonstrated by intradermal injection of streptococcal antigen. Cutaneous reactions indicating antigen were greatest during the active stage of the disease, became less marked as active symptoms subsided and as antibody increased, and both became slight or absent during the quiescent stage.

Intravenous therapeutic injections of histamine, and especially of histamine and thermal antibody as given under Dr. Horton's supervision,<sup>3</sup> and the thermal antibody and antigen, or vaccine without histamine, caused a diminution of antigen and an increase in antibody and apparently a concomitant improvement in symptoms in persons during the active stage of multiple sclerosis. A nonspecific and specific means for treatment seem at hand. Due regard to the prevention of respiratory infection and to a consideration of foci of infection, especially in teeth and tonsils, is indicated.

The cause of death in animals in which cultures of the brain revealed the streptococcus seemed clear, but in those that died after the streptococcus was no longer isolable from the brain or blood, and no longer demonstrable in the lesions simulating in this respect what occurs in multiple sclerosis.

sclerosis, the cause of death was obscure. Attempts were made to explain this phenomenon. The evidence adduced indicates that fatalities in the experimental and naturally occurring disease, in the absence of living streptococci, may be due to the formation of a streptococcic neurotoxin having predilection for vital nerve centers, and to which vital centers become allergic; and perhaps to the formation of an autogenous sensitizing streptococcal-nerve-tissue complex which may function in a manner similar to the wholly foreign adjuvant-nerve-tissue complexes used successfully by others in the production of "allergic" encephalomyelitis.<sup>4,5</sup>

The possibility of a virus etiology has not been sufficiently studied. The data obtained indicate that a green-producing or alpha streptococcus of low general virulence, having specific localizing, toxicogenic and antigenic properties, is etiologic in multiple sclerosis.

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# RH FACTOR IN IMMUNOLOGICAL REACTIONS

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THE purpose of this paper is to present briefly some fundamental facts of importance to the field of immunology in general, which were unearthed as a result of studies on sensitization to the rhesus factor. In this preliminary report it is also intended to point out some of the applications of these findings to immunology in general, and to allergy in particular.

As is well known, the discovery of the Rh factor by Landsteiner and Wiener,<sup>16,17</sup> was followed in rapid succession by the demonstration by Wiener and Peters<sup>34</sup> of the rôle of this blood factor in the causation of intragroup hemolytic transfusion reaction, and the brilliant work of Levine, Burnham, Katzin and Vogel<sup>5,10</sup> in establishing the part played by the Rh factor in the pathogenesis of erythroblastosis fetalis. In these early studies, it was assumed that the antibody responsible for Rh sensitization was the Rh *agglutinins*, but it was soon found that there was a lack of correlation between the severity of the clinical manifestations and the titer of the Rh agglutinins, and in the most severe cases usually no Rh agglutinins at all were demonstrable in the patient's serum. This was incorrectly ascribed at first<sup>20,35</sup> to the supposed action of Rh antibodies fixed to tissue cells, but the mystery was finally solved by the discovery of the so-called Rh blocking antibody.<sup>36,27</sup>

As has been demonstrated elsewhere,<sup>36,37</sup> Rh-negative individuals sensitized to the Rh factor may produce either or both of two kinds of specific antibodies, namely, agglutinins and glutinins (or blocking antibodies). Because of their ability to clump Rh-positive cells directly, in saline as well as serum media, the Rh agglutinins are considered to be bivalent (or multivalent) in the chemical sense. On the other hand, glutinins (blocking antibodies) merely coat Rh-positive cells in saline media without clumping them and are therefore considered to be univalent. In plasma (or serum) media, univalent Rh antibodies can clump Rh-positive red cells with the aid of a third component, conglutinin, present in such media.

Based on these concepts of the nature of agglutinins and glutinins (blocking antibodies), it seemed reasonable to presume that agglutinins are comprised of larger molecules than glutinins or blockers.<sup>38,39</sup> This is supported by studies on the permeability of the human placenta to alpha, beta, and Rh antibodies which showed that univalent antibodies (glutinins or blockers) readily passed through the intact placenta into the fetal circulation, while agglutinins failed to traverse this barrier.<sup>40,41</sup> These studies were made on only a few cases, and it is proposed now to report a larger series of cases of Rh sensitization.

From the Serological Laboratory of the Office of the Chief Medical Examiner of New York City, and the Blood Transfusion Division of the Jewish Hospital of Brooklyn, N. Y.  
A preliminary report, based on a lecture presented before the American College of Allergists on March 12, 1948.

# RH FACTOR—WIENER

TABLE I. COMPARISON OF THE TITERS OF RH ANTIBODIES IN THE MATERNAL SERUM AND IN THE CORD SERUM OF RH-NEGATIVE INFANTS AT BIRTH

Case No.	Titer (units†) of Maternal Serum by		Titer (units) of Cord Serum by	
	Agglutination Method	Conglutination* Method	Agglutination Method	Conglutination* Method
1	0	20	(a† 0 b† 0	18 22
2	0	7	0	7
3	0	22	0	20
4	0	44	0	48
5	0	22	0	22
6	0	15	0	10
7	24	11	0	2½

\*In albumin-plasma mixture.

†Twins.

‡The values given represent the average of the results of 2 or more titrations.

## MATERIALS AND METHODS

This report is based on a series of cases in which Rh-negative women who had previously had erythroblastotic babies gave birth to normal Rh-negative babies. The maternal Rh antibody titer was determined periodically during the pregnancy, and at delivery a sample of the infant's blood was obtained from the umbilical cord vessels and another sample of the maternal blood for comparative titrations. All titrations were carried out by the saline agglutination and albumin-plasma conglutination methods, as previously described,<sup>30,12</sup> against group O blood cell suspensions of types Rh<sub>1</sub> and Rh<sub>2</sub> as well as control cells of type rh. Thus, the titer values given in this report represent averages of at least two titrations, and often as many as four or more titrations.

Parenthetically, it should be mentioned that in our hands the various methods of titrations used had a technical error of about one tube, or 100 per cent, when performed on different days, using test cells of different freshness and sensitivity and plasma of different conglutinating activity. Thus, a serum with a titer of 50 units might give values in different tests ranging from 25 to 100 units on different days. Therefore a four-fold difference in titer from one determination to another did not necessarily mean that there had been any real change in titer, and only by repeating titrations at frequent intervals could one overcome the misleading impression caused by such accidental variations in titer values. None of our Rh-negative patients carrying Rh-negative babies showed any significant change in titer during their pregnancies, and claims by other workers that "anamnesic" rises in Rh antibody titer can be induced by Rh-negative fetuses are possibly based on the incorrect interpretation of such illusory observations.

In a few cases, additional samples of blood were obtained at monthly intervals from the infants by venepuncture, in order to determine the length of time after birth that the maternal Rh antibodies persisted in the infant's circulation.

## RESULTS

In Table I are presented the results of determinations of Rh antibody titers of the sera of seven Rh-negative women and their Rh-negative infants at the time of birth. In six cases, the maternal serum failed to clump

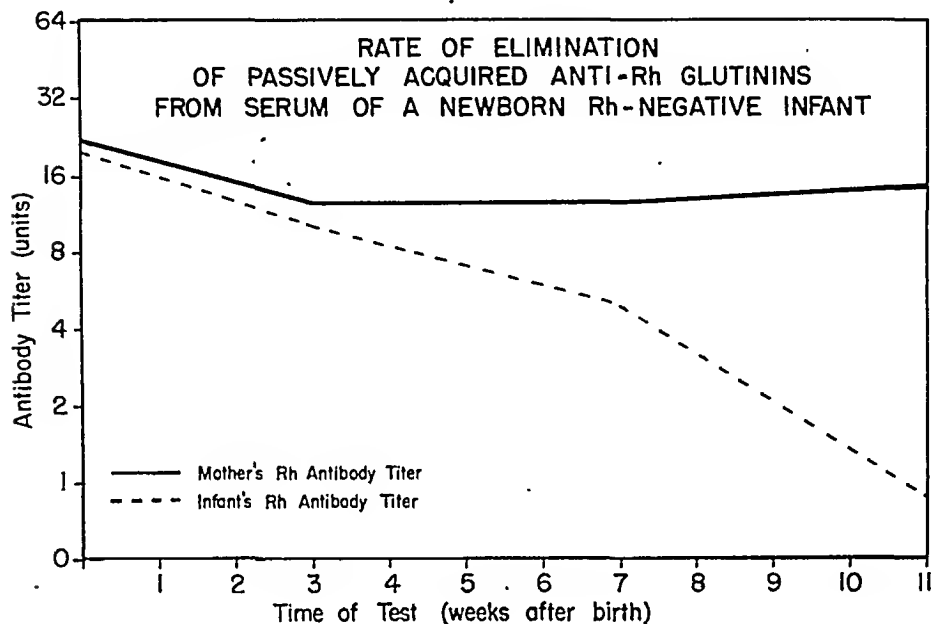


Fig. 1.

Rh-positive cells in saline media but strongly clumped such cells in plasma media, i.e., the sera of these women contained Rh glutinins with little or no accompanying Rh agglutinins. It will be seen that in these six cases the serum of each infant gave the identical titer of its respective mother's serum,\* indicating that there had been a free passage of antibodies through the placenta into the fetus *in utero* until the antibody titers on both sides of the placenta became equal. Case 1 is of special interest since it involves a pair of Rh-negative twins. Case 3 is important because it involves a premature infant born six weeks before term and weighing less than 5 pounds. It will be seen that even at this early date, the fetal antibody titer was equal to the maternal antibody titer, demonstrating that, in this case at least, univalent antibodies readily passed through the placenta as early as six weeks before term, and probably considerably earlier.

In Case 7, the maternal serum contained a potent anti-Rh agglutinin, but no agglutinin was present in the infant's serum—only a very weak glutinin. Thus the placenta acts toward antibodies like a semipermeable membrane, by holding back agglutinins, but permitting glutinins (blocking antibodies) to pass freely. This supports the writer's thesis that whatever

\*The excellent agreement between the titers of maternal and infant's sera is due to the performance of the tests in parallel on the same day, using the same test cells and albumin-plasma mixture.

agglutinins (bivalent antibodies) pass from mother to infant probably do so through some placental defect, and also possibly at parturition when the increased intra-uterine pressure may help to milk such antibodies into the fetus.

In Case 3, comparative studies were made of the mother's and infant's Rh antibody titers at monthly intervals after the delivery. As shown in Figure 1, there was no significant change in the maternal antibody titer during the period of four months when the studies were continued, but the Rh antibody titer of the infant's serum gradually fell, so that only traces were demonstrable by the end of the fourth month. Due to lack of cooperation of the patients, similar detailed studies could not be done in the other cases. In Case 4, however, it was found that while there was no significant change in the infant's antibody titer after one month, the titers were about one-third their original values at the end of the second month. In Case 2, tests at the end of the third month showed no change in the maternal Rh antibody titer while the infant's serum contained only traces. These observations indicate that, in general, the univalent antibodies passively acquired by the infant from its mother persist in the baby's circulation for periods of about four months on the average.

#### SIGNIFICANCE OF FINDINGS IN RELATION TO THE PATHOGENESIS OF ERYTHROBLASTOSIS

The observations on placental transfer of Rh antibodies have served to clarify the puzzle of the pathogenesis of erythroblastosis. The offending antibody is evidently not the Rh *agglutinin*, as postulated by Levine,<sup>19,20</sup> but the Rh *glutinin* (blocking antibody).<sup>37,43,44</sup> Of course, Levine was not in a position to arrive at the complete explanation, since the Rh blocking antibody was found *after* his theory was proposed. That the univalent antibody is the important antibody is supported by recent observations which show a close correlation between titer of univalent antibodies in the maternal serum antenatally and the severity of the manifestations in the erythroblastotic fetus or baby.<sup>8,26,29,45</sup> The Rh agglutinins apparently play, at most, a secondary rôle in the pathogenesis of erythroblastosis, because they cannot enter the fetal circulation except through a placental defect, though a small amount may be milked into the fetus during labor as a result of the increased intra-uterine pressure.

Accordingly, the presence of Rh agglutinins in a patient's serum antenatally has significance only in indicating that the prospective mother has been sensitized, and that therefore her serum may also contain univalent Rh antibodies (glutinins or blockers) which are of importance in the pathogenesis of erythroblastosis. Cases have been encountered<sup>46</sup> where the maternal serum contained potent Rh agglutinins, yet the infant born, though Rh-positive, was normal or only mildly erythroblastotic. It is now clear that in these cases the maternal serum must have contained little or no univalent antibodies. On the other hand, we have encountered no

case with a significant titer of univalent antibodies antenatally, in which an entirely normal Rh-positive infant was subsequently born.

Thus, according to the new concept, the pathogenesis of typical erythroblastosis is traced to univalent antibodies in the maternal serum, with agglutinins playing, at most, a secondary rôle. This applies not only to cases caused by Rh sensitization but also to instances of A, B, Hr and other sensitizations.

#### SIGNIFICANCE OF FINDINGS FOR THE PROBLEM OF NEONATAL IMMUNITY

While the passive transfer of Rh antibodies from mother to fetus serves no useful purpose, but is harmful instead to the fetus with Rh-positive blood, it provides a clear though perverted example of the mechanism of neonatal immunity in general. There now seems but little doubt that whatever immunity the infant possesses during its neonatal period can be attributed to antibodies (usually glutinins or blocking antibodies and not agglutinins) passively acquired by the fetus *in utero* by transplacental transfer.<sup>†</sup> A practical application of this fact is in the antenatal selection of donors for exchange transfusions to erythroblastotic infants.<sup>47,48</sup> For example, group B donors may be used for group O as well as group B babies born to group B mothers, because such infants will have no beta antibodies in their sera. Another application is in the diagnosis of congenital syphilis, for which purpose serological tests on cord serum are of little value, since such tests merely constitute an indirect way of examining the maternal serum. The present study confirms other reports that the neonatal immunity passively acquired by the infant from its mother usually persists for about four to six months.<sup>3,15,56</sup>

In connection with this problem, it is of interest to discuss the work of Adams, Kimball, and Adams<sup>1</sup> who immunized expectant mothers with pertussis vaccine and then compared the antibody titers of the maternal serum and the infant's umbilical cord serum at birth. In many cases the maternal and fetal antibody titers were equal, e.g., both 320 units; in other seemingly comparable cases (maternal titer 320 units) little or no antibodies were demonstrable in the umbilical cord serum. These observations can now be readily explained by postulating that the maternal serum in the former type of case contained glutinins, while in the latter type of case the antibodies were agglutinins. Evidently, the technique used by these authors was such that it detected both agglutinins and glutinins indifferently.

If one were to inquire as to the "reason" for the infant's dependence on the maternal antibodies for its neonatal immunity, one finds that this is due to the inability of the fetus and newborn infant to produce their own antibodies, reflecting the immaturity of the antibody-forming cells during this period of life.<sup>1,10,56</sup> This is closely related to the observation of Lewis and Wells,<sup>22</sup> who showed that the blood serum of young animals

<sup>†</sup>Observations on transplacental transfer of antibodies in animals are not always applicable to man, because of anatomical differences in the structure of the placenta.<sup>16</sup>



is deficient in globulin, apparently because of lack of capacity to form such proteins.

The principles involved are well illustrated in a recent case of erythroblastosis treated by exchange transfusion.<sup>49</sup> In this case both parents were group B, and because the expectant father belonged to type Rh<sub>1</sub>Rh<sub>1</sub> and the expectant mother to type rh with potent Rh blocking antibodies in her serum, the infant was delivered six weeks before term by cesarean section, and immediately treated by exchange transfusion with 1,000 c.c. of Brh blood. It was later found that the infant belonged to group O. Nevertheless, the group B blood survived normally in the baby's circulation. In fact, for a period of thirty days the only red cells present were the group B cells received by transfusion. Thereafter, the group B cells were gradually replaced by the infant's own group O cells, and it was not until four months had passed that all the group B cells had been eliminated. Even at this late date, no anti-A or anti-B agglutinins were demonstrable in the baby's serum, even though the baby had been subjected to the most potent antigenic stimulation possible, namely, the complete replacement of its own group O cells by group B red cells. A subsequent test at the age of six months still showed only barely demonstrable alpha and beta antibodies of one unit titer. This demonstrates in striking fashion the immaturity of the antibody-producing mechanism in the newborn and accounts for the dependence of the infant during its neonatal period on antibodies passively acquired from the mother. This also indicates the futility of initiating vaccine injections in newborn infants before the fourth month, in conformity with Sauer's observations.<sup>30</sup>

#### NATURE OF THE DIFFERENCES BETWEEN UNIVALENT AND BIVALENT ANTIBODIES

In the most recent edition (1946) of one of the leading texts on immunology,<sup>52</sup> the following appears: "The view that precipitins, opsonins, antitoxins, et cetera, differed in kind, held the field for many years, but the unitarian hypothesis that these are due to the same kind of antibody in different circumstances has now gained almost universal acceptance. . . . This conception of the serum reactions does not, of course, modify our belief in the multiplicity of antibodies corresponding to a multiplicity of antigens. A red cell, a bacillus, a crude protein solution such as horse serum, contains many antigens and gives rise to many antibodies. The unitarian hypothesis, as Zinsser (1921) has emphasized, implies that the injection into the tissues of a chemically pure antigen will lead to the formation of one antibody capable of producing various manifestations of antigen-antibody union." This quotation is repeated here since it serves to emphasize the fact that the discovery<sup>36,57</sup> that Rh-negative patients sensitized to the Rh factor may form two sorts of antibodies, is the first clear disproof of the unitarian hypothesis. That the significance of this evidence is not fully appreciated by other workers in the field is shown by the

# RH FACTOR—WIENER

TABLE II. DIFFERENCES BETWEEN "UNIVALENT" AND "BIVALENT" ANTIBODIES

Characteristics	Bivalent Antibodies	Univalent Antibodies
Common names*	Agglutinin	Glutinin; blocking antibody
Usual time of appearance in course of immunization <sup>9</sup>	Early	Late
Resistance to heating <sup>9, 14, 31</sup>	Relatively thermolabile	Relatively thermostable
Reaction with cells† in saline media	Clumps cells by agglutination	Coats cells without clumping them
Reaction with cells in plasma or serum media	Clumps cells by agglutination	Clumps cells by conglutination
Nature of clumps	Easily dislodged from glass surface	Tend to adhere to glass surface
Specificity of clumps	Specific—clumps contain only one type of cell	Non-specific—clumps may contain more than one type of cells
Rôle in erythroblastosis	Minor	Major
Reaction with cells in presence of complement <sup>34</sup>	Does not fix complement or lyse cells	Fixes complement and lyses cells
Behavior relative to placenta	Held back by the intact placenta	Passes through with relative ease
Role in allergy <sup>22a, 30a</sup>	Sensitizing antibody	Blocking antibody
Role in immunity	Precipitating antibody	Protective antibody

\*Distinguishing names have not yet been devised for univalent and bivalent precipitins.

As Landsteiner<sup>18</sup> points out, however, agglutination is equivalent to a precipitation reaction on a surface.

†Red cells, bacteria, spores and so on.

frequent use of the misnomer "incomplete agglutinins" for the univalent antibodies,<sup>27</sup> and the avoidance by some workers of the terms "conglutination" and "conglutinin" and the substitution of the vague expressions "agglutination enhancing action of serum" and "agglutinin activating principle in serum."

There can no longer be any doubt that univalent antibodies and bivalent antibodies are quite distinct entities, as shown by the fact that they can be sharply separated by natural means such as placental filtration.<sup>40, 41</sup> Moreover, a partial separation of these antibodies has been effectuated by Witebsky et al,<sup>53</sup> using the method of dialysis in cellophane bags against distilled water. While the agglutinin proved to be associated principally with the resulting precipitate which contained most of the globulins, the blocking antibody remained mostly in the supernatant fluid together with the albumin. Incidentally, this procedure may prove of value in the antenatal diagnosis of erythroblastosis in cases where the prospective mother's serum contains agglutinins, because it may make possible the unmasking of univalent antibodies which Wiener has shown to be of major importance in the pathogenesis of erythroblastosis fetalis.\*\* Moreover, the successful separation of the two sorts of antibodies by dialysis further supports the concept that agglutinins (bivalent antibodies) are composed of larger molecules than blocking antibodies (glutinins, univalent antibodies).

In the first papers on Rh blocking antibodies,<sup>36, 37</sup> it was pointed out that

\*\*A still simpler procedure, which makes use of the difference in resistance to heating of the two sorts of antibodies, has recently been devised by the writer.

the observations made were of general immunological significance and should be applicable to other antigen-antibody systems. In fact, the principles have already been applied successfully to the study of the antibodies of infectious mononucleosis,<sup>21</sup> brucellosis,<sup>22</sup> and other diseases. The major problem in further extending these applications will be to prepare satisfactory emulsions of the antigens for use in the agglutination and conglutination tests.

Since it is important to know the nature of the differences which exist between univalent and bivalent antibodies, in Table II the present information and concepts regarding this aspect of the problem have been summarized. Some of the references given are to the older literature, which has been reinterpreted in terms of the newer concepts.

#### OTHER APPLICATIONS IN IMMUNOLOGY

The newly available information regarding univalent and bivalent antibodies can be applied to the solution of a number of problems:

1. For a long time it has been observed that there is only an incomplete correlation between the titer of the isoagglutinins, alpha and beta, and the ability of the serum to lyse specifically red cells containing agglutinogens A and B, respectively, so that occasionally sera with low agglutinin titers lyse such cells while some sera with relatively high agglutinin titers fail to lyse such cells.<sup>47</sup> This is now readily understood, since the isoagglutination reaction is attributed to alpha and beta *agglutinins* (bivalent antibodies), while isohemolysis is ascribed to alpha and beta *glutinins* (univalent antibodies) in the presence of complement. Some correlation between agglutinin titer and isohemolysis is to be expected, because the sera with the most potent agglutinins will usually be derived from immunized individuals and would therefore be more apt to contain strong glutinins.

2. In studies on treated syphilitic mothers who were subsequently delivered of nonsyphilitic infants, different investigators have obtained conflicting results when comparing the reagin content of the maternal and umbilical cord sera.<sup>25</sup> This is now readily explained by differences in the methods of titrating syphilitic reagin used by the different investigators. Where complement fixation methods (detecting univalent antibodies) are used, the titers obtained for maternal and infant's sera would be expected to be equal, but where methods are used which detect principally bivalent antibodies the newborn's serum may show little or no reagin despite a high titer in the maternal serum.

3. To account for the pathogenesis of acquired hemolytic anemias, the writer<sup>47</sup> has suggested that in rare susceptible individuals, when an acute breakdown of red cells occurs, as in sulfonamide therapy, benzene poisoning, malaria, certain influenzal infections (virus attached to red cells), trauma (hematomata), et cetera, the released stromata act as antigens and induce the formation of auto-antibodies which act on unaltered red cells.

This produces more hemolysis, and the hemolyzed cells in turn induce more antibody formation so that a vicious cycle results. Luckily, such auto-immunization is extremely rare, and hemolytic injuries are usually self-limited in their effects. In the rare susceptible individual where auto-sensitization results, recovery is very infrequent. In support of this hypothesis may be cited a number of cases<sup>4,33,50</sup> in which it was possible to demonstrate in the patient's serum auto-agglutinins which differ from the natural auto-agglutinins in that they are equally active at body, room and refrigerator temperature, while the natural auto-agglutinins are cold agglutinins. Until recently, however, it was not possible to demonstrate the presence of auto-antibodies in the great majority of cases of hemolytic anemia, and this has now been explained because auto-antibodies like other antibodies may be of the univalent type. The univalent auto-antibodies coat the patient's own blood cells so that a condition results which simulates that which exists in erythroblastotic infants. Coating of the patient's cells by auto-antibodies can readily be demonstrated by the same techniques used for the diagnosis of erythroblastosis fetalis, namely, the conglutination test<sup>38</sup> and the antiglobulin test.<sup>25,32,40</sup> In malaria this process accounts for the rare complication of "blackwater fever," or if the cells clump by conglutination instead of hemolyzing, death from cerebral malaria may result, a syndrome somewhat analogous to nuclear jaundice in the erythroblastotic infant.

The natural auto-agglutinins are qualitatively different from the immune auto-antibodies, and the former probably depend on certain peculiarities of normal serum globulin as against immune globulins. The rise in cold auto-agglutinin titer associated with virus pneumonia therefore probably reflects an increase in the normal serum globulins due to nonspecific irritation of the antibody-forming cells. The hemolytic anemia<sup>2,11,55</sup> that sometimes results when the cold auto-antibodies are of such high titer that they also react at body temperature differs from the acquired hemolytic anemia described above in that complete recovery is the rule, following simple transfusion therapy.<sup>40</sup>

4. In the conglutination test for coating of erythrocytes by univalent antibodies (Rh antibodies, auto-antibodies, or antibodies of other specificities), all that is necessary is to suspend the cells in plasma or albumin-plasma mixture and spontaneous clumping results because the conglutinin present in the plasma is adsorbed by the sensitized cells and completes the reaction.<sup>38,45</sup> The antiglobulin technique depends on a different principle,<sup>6,7,24,51</sup> namely, the use of a rabbit precipitin against human serum which reacts with the human globulin (the specific univalent antibody) coating the red cells, thus causing them to clump together. It is not generally appreciated that the antiglobulin reaction is an agglutination reaction, and if the precipitin serum contains univalent antiglobulin antibodies instead of bivalent antibodies, the test may fail. The intelligent application of the

newer knowledge of univalent and bivalent antibodies is therefore essential for the successful use of the antiglobulin technique.

#### APPLICATIONS IN ALLERGY

In closing, some possible applications of these newer concepts to some problems in allergy, especially the pathogenesis of infantile eczema, will be pointed out, with the hope that this may stimulate new investigations which may help solve this enigma.

The work of Sherman, Hampton and Cooke<sup>30a</sup> leaves hardly any doubt that the skin-sensitizing antibodies are bivalent antibodies, while the blocking antibodies of allergy are univalent antibodies (Table II). Thus, these workers found that skin-sensitizing antibodies do not pass the placental barrier, while blocking antibodies pass through freely into the fetus. That the failure of maternal skin-sensitizing antibodies to pass into the fetus is not due to fixation of the antibodies by the placenta is indicated by the observation that placental extracts are free of such antibodies. Loveless<sup>22a</sup> showed that skin-sensitizing antibodies (reagins) are thermolabile, while blocking antibodies are relatively thermostable. Moreover, Cooke, Loveless and Stull<sup>7a</sup> found that maternal blocking antibodies passively acquired by the infant disappear from its serum within three to six months, while the antibodies disappear from the maternal serum much more slowly. The parallelism between the observations in the fields of allergy and Rh sensitization further justify the term "Rh blocking antibody" in preference to other terms, such as "incomplete Rh antibody," that have been suggested by other workers.

Based on these observations and in line with the newer concepts, the following definitions are offered.<sup>13,52</sup>

1. The normal (nonallergic and nonimmune) state is that in which the body contains no *induced* antibodies specific for the antigen in question. Cognizance is taken of the possible presence, however, of so-called natural or normal antibodies.<sup>18</sup>

2. The immune state is one in which the body has acquired large amounts of antibodies of the blocking type, formed in response to the introduction of antigen into the body by either natural or artificial means, so that there is an excess of univalent antibodies free in the plasma and other body fluids.

3. In the allergic state, the body contains sensitizing (bivalent) antibodies attached to cells, with little or no free univalent antibodies in the body fluids. Reagin represents excess bivalent antibodies free in the body fluids.

4. Hyposensitization is the process of converting the allergic state into the immune state by repeated injections of antigen at sufficiently wide intervals to stimulate the production of potent blocking antibodies. This treatment is successful only when the subject achieves an adequate level of free univalent antibodies in his or her body fluids.

5. Desensitization consists in the injection of progressively increasing doses of specific antigen in rapid succession in order to saturate antibodies attached to body cells. This method, besides being dangerous, is often unsuccessful, and the refractory state that ensues is only temporary due to the subsequent production by the body of additional antibodies.

Before describing the application of the newer concepts to infantile eczema, some other pertinent observations will be presented. Experiments<sup>46</sup> with the production of anti-Rh typing sera, by injecting Rh-positive blood into Rh-negative male volunteers, reveal that the majority of those who respond show only univalent antibodies (glutinins or blockers) in their sera, while only a small minority produce agglutinins. Moreover, when the injections are continued any agglutinins which may have been formed are eventually largely or completely replaced by blocking antibodies. Thus, bivalent antibodies, if they are formed at all, are usually produced only early in the course of the immunization. Once a person has been sensitized to the Rh factor, and the antibody titer has fallen with the passage of time, the injection of a relatively minute amount of antigen is usually sufficient to elicit a pronounced antibody response. In line with this, Cooke, Loveless and Stull<sup>47</sup> found that normal subjects required much more pollen extract (200,000 to a million units) to produce blocking antibody than hay-fever patients sensitized to ragweed (total 4140 units).

Previous studies have revealed that the predisposition to allergic diseases is hereditarily transmitted. In persons homozygous for the abnormal gene, the age of onset is usually in the period before puberty, and these individuals make up the bulk of the cases of infantile eczema and asthma.<sup>51a</sup> That the effect of the abnormal gene can be modified follows from the observation that twice as many males as females develop allergic disease before puberty. In persons heterozygous for the abnormal gene, allergy may never appear in typical form (carriers), but about one-fifth of these individuals exhibit allergic symptoms usually after puberty—these constitute the bulk of the cases of hay fever.<sup>51a</sup>

The mother and also the father of the baby with infantile eczema are therefore themselves allergic or at least carriers of the abnormal gene. For example, in cases of infantile eczema due to sensitization to wheat, the constitutionally predisposed infant, when fed foods containing this antigen produces bivalent (sensitizing) antibodies for wheat. While the infant's mother will usually be hyposensitive to wheat, any univalent antibodies against wheat passively acquired by the infant by placental filtration will have been lost by the third or fourth month, when it is likely for the first time to produce its own sensitizing antibodies. This would account for the delayed onset of infantile eczema, usually until several months after birth. Permanent cure of this disease takes place only when the infant's body is stimulated, either by natural or artificial means, to produce wheat antibodies of the blocking type, so that an excess of these antibodies is

again present, free in the body fluids. The eventual production of such antibodies accounts for the spontaneous cure of infantile eczema, usually by the time the second year is reached.

It is too early to discuss other applications of these new concepts in the field of allergy, until more accurate quantitative data are compiled concerning the titers of reagin and blocking antibody in different allergic conditions. For this purpose, the classic method of titration using increasing antigen dilutions is not satisfactory, because antibody titers can be determined reliably only by testing increasing dilutions of serum against a fixed quantity of antigen.

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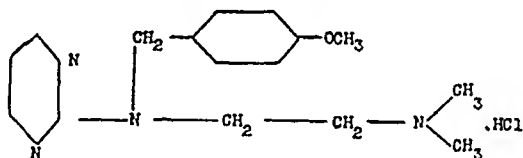
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# CLINICAL EVALUATION OF NEOHETRAMINE, A NEW ANTIHISTAMINE

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A GREAT deal of literature has accumulated in recent years on the action of the new antihistaminic drugs. It is generally recognized that they control various allergic manifestations, notably those of urticaria and vasomotor rhinitis. They appear to counteract such action of histamine as whealing, bronchospasm, secretion of salivary and bronchial glands.

We have had occasion to carry out clinical trials with Neohetramine,\* a new compound. This is an ethylenediamine derivative, highly soluble and relatively stable in aqueous solutions. Its chemical formula is 2-(N-dimethylaminoethyl-N-p methoxybenzyl)-aminopyrimidine monohydrochloride.



## EXPERIMENTAL DATA

Laboratory experiments carried out by Scudi, Reinhard and Dreyer<sup>1</sup> generally, followed the procedures devised in evaluating other antihistaminic drugs. Guinea pigs and rabbits were fully protected against otherwise lethal doses of histamine. The drug was administered intraperitoneally fifteen minutes before aerosol insufflation of histamine into the bronchi and, in other experiments, before intravenous injections of histamine. Neohetramine prevented anaphylactic shock in actively and passively sensitized guinea pigs. It counteracted the fall in blood pressure ordinarily encountered from intravenous injections of histamine as well as dilatation of capillary blood vessels. In comparison with other antihistaminics tested, Neohetramine appeared to be of low toxicity.

## CLINICAL OBSERVATION

Observations were made on 279 allergic patients. In selecting these cases for the clinical trial, an attempt was made to exclude those who exhibited evidence of secondary infection. It had been noted before that infection, superimposed upon the allergic symptoms, reduced the benefit obtained from antihistaminic drugs considerably. Some of the patients were observed in the clinic for several hours after they had taken the drug; in most cases, however, our conclusions were based on careful questioning within one to two days after the treatment was started. Doses of 50 mg. were employed at four-hour intervals. The patients were instructed to take the

<sup>1</sup>From the Allergy Clinic, Out-Patient Department, Harper Hospital, Detroit, Michigan.

\*Supplied by Nepera Chemical Co., Inc., Yonkers, N. Y., and now distributed by Wyeth, Inc.



drug only when symptoms were present. Nearly all had previously had other antihistaminic medication and were able to compare the new drug with them. Forty-eight patients received placebo tablets containing  $\frac{1}{4}$  grain of phenobarbital, alternating with the new drug in order to enable us to evaluate the possibility of a psychogenic effect from the drug.

TABLE I

Diagnosis	Total	Results			
		None	Slight	Good	Side Effects
Bronchial Asthma	75	42 (56%)	20 (27%)	13 (17%)	9
Allergic Rhinitis and Hay Fever	165	52 (32%)	50 (30%)	63 (38%)	17
Urticaria	21	3	6	12	—
Migraine	5	2	2	1	—
Atopic Eczema	6	2	2	2	1
Contact Dermatitis	2	2	—	—	2
Allergic Conjunctivitis	5	3	2	—	—
Total	279	106	82	91	29 (10%)

Table I presents our results. Where the drug was effective, the improvement started within thirty minutes and lasted approximately four to six hours. After this interval, symptoms recurred.

Urticaria and allergic nasal disease showed the best results. Eighteen (86 per cent) out of twenty-one patients with urticaria and 113 (68 per cent) out of 165 patients with a seasonal and perennial allergic nasal disease were benefited. In the group of patients with asthma, thirty-three (44 per cent) out of seventy-five showed some degree of improvement. Only three (13 per cent) out of twenty-one patients with urticaria and fifty-two (32 per cent) out of 165 with seasonal and perennial allergic nasal disease were not benefited. On the other hand, in the group of patients with asthma, only thirteen (18 per cent) showed some improvement. In the other allergic conditions in which the drug was employed, namely, atopic eczema, contact dermatitis, migraine headaches and allergic conjunctivitis, too few patients were treated by us to draw definite conclusions. It is evident, however, from Table I that the results simulate closely those obtained with other antihistamine drugs.

In twenty-nine (10.4 per cent) out of 279 patients, side effects were encountered which resembled those observed with the other drugs. The side effects, however, were less frequent. Dizziness and drowsiness were most prominent. Several patients presented muscular twitching about twenty minutes after ingestion of the drug, which disappeared spontaneously in approximately one hour.

One of our patients (Mr. F. R.) with urticaria, was given 50 mg. of the following six drugs on successive days in the office: Neo-Antergan, Trimection, RP-3277, Antistine, Benadryl and Neohetramine. Within one-half hour following the ingestion of each, he developed marked drowsiness and sleepiness. During his sleep he exhibited marked muscular twitching of the limbs and trunk, which at times resembled epileptic attacks. This lasted for

(Continued on Page 316)

## DERMATOPHYTOSIS AND FUNGUS SENSITIVITY

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**D**UE to the relative increase both in severity and in number of cases of dermatophytosis and dermatophytids seen during the past year, our interest was stimulated in the search for a more satisfactory treatment. The long list of accepted local therapeutic measures did not offer the gratifying results that ordinarily we would have expected from close observation and control of our patients. No one method of local therapy seemed to be uniformly successful. In many, a great variety of medications had to be used in order to obtain any results. Often during the long tedious process of determining the effective therapeutic agents, the patient suffered a spontaneous remission of the disease. In most instances, the patient soon returned with a recurrence of the disease.

A number of the patients presenting themselves for treatment were veterans of World War II, which is not surprising in view of the American Medical Association's report by the Council of Pharmacy and Chemistry, "The War and Dermatophytosis,"<sup>1</sup> in which it was revealed that 8 per cent of all army hospital admissions were for cutaneous disease and that dermatophytosis ranked second highest as cause for these admissions.

Delaney<sup>2</sup> feels that about 80 per cent of all personnel stationed in the South Pacific area for more than three months contracted a fungus infection of some type.

Almost universally, these patients had histories of long-standing infections with special reference to their primary lesion. Most had developed the secondary dermatophytids which appeared of greater severity than the primary lesion. In a number of cases the "id" (dermatophytid) lesions were of such nature as to cause a definite disability and a major physical disfigurement. The "id" lesions are variable in presentation but are generally characterized as erythematous, irregular, papular or vesicular lesions, nodular in the more acute stages, becoming more eczematoid or psoriatic-like in the chronic form. In a few cases where the "id" lesions were severe, the primary lesions, usually on the hands or feet, were concomitant causes of complaint.

It has been our experience that a patient will present himself with a history of having been treated with at least ten different types of local medications plus an unsuccessful course of x-ray therapy. These patients have developed a strong psychogenic complex because their chronic lesions do not seem to respond to the best of available local therapy in spite of their eager co-operation.

There seems to be no question that dermatophytosis has been a thera-

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<sup>1</sup>From the Allergy Clinic, St. John's Riverside Hospital, Yonkers, New York.

peutic problem for many years, and there are many reports consistent with the findings of Weidman,<sup>29,30</sup> showing that 67 per cent of 100 medical students were infected and had primary lesions which yielded positive cultures in 57 per cent. A more recent survey reported by Lewis and Hopper<sup>16</sup> of 1,399 cases, revealing positive slides in 46 per cent and positive cultures in 67.3 per cent. These surveys and those of Duemling,<sup>5</sup> Delaney,<sup>4</sup> Montgomery and Casper<sup>18</sup> also illustrate that the offending organisms in the majority of cases are the trichophytons, with the epidermophytons ranking second and the monilias third. Over an eleven-year period, 1935 through 1945, at the New York Skin and Cancer Unit, 17.9 per cent of the 1,706 positive cultures were isolated from lesions of the feet, and 30.5 per cent of the 331 taken from the hands were of the *Trichophyton* group of fungi.

With a large proportion of our population returning to civilian status from service with the armed forces, many of whom were in tropical areas, it is possible that the evolution of this clinical entity can result in a grave medical problem should the present trend continue.

Having these thoughts in view, it became obvious that this disease had to be approached from the immunologic point of view. Although the fungi are ubiquitous in nature, there seems to be no question that they are abundant, are etiologic agents and can cause cutaneous disease. The Association of Allergists on Micrological Investigation<sup>31</sup> has uncovered a variety of fungi which are definitely causative factors of allergic disease. It is unfortunate to contemplate that comparatively little work has been directed toward these universal and abundant pathogens. Extensive surveys have been reported by Durham,<sup>6,7</sup> Feinberg and Little,<sup>10</sup> Wittich<sup>32</sup> and others. It has been proven that fungi are not only air-borne so as to cause hay fever and asthma, but are also found abundantly in the smuts and rusts. These same fungi can and do cause serious dermatologic lesions.

Even though the fungi are not considered virulent pathogens, they can be transferred from human to human as well as from animals to humans and thus can cause the spread of disease, reaching epidemic proportions. Many types of fungus dermatoses are endemic in various parts of the United States. Dermatophytosis can be a grave disease and is of serious import. Other fungus diseases, such as actinomycosis, histoplasmosis and blastomycosis, can be fatal.

The immunologic aspect of fungus infection has been known for some time. The work of Low,<sup>17</sup> Block,<sup>2</sup> and Jadassohn and Peck<sup>14</sup> has been confirmed, giving evidence that a skin hypersensitivity develops to the fungi of the trichophyton group quite constantly when these organisms are present in superficial tinea infections of the hands and feet. There seems little question that fungi can cause chronic eczematoid lesions, as shown by Hilgermann<sup>12</sup> and confirmed by more recent work of Hopkins, Benham and Kesten,<sup>11</sup> who found a definite sensitization to saprophytic

fungi in deep-seated eczematoïd lesions. Brown<sup>8</sup> skin-tested patients with chronic eczemas and found them sensitive to a variety of fungi; the lesions cleared up when the fungi were eliminated from the environment or were specifically treated. Skin lesions, according to Henrici<sup>11</sup> are typical characteristics of hypersensitivity in fungus diseases.

Sulzberger,<sup>23</sup> working in Block's clinic, has demonstrated that there is a spontaneous passage of formed elements (spores) of fungi originating from the primary lesions by hematogenous dissemination. These formed elements can cause eczematoïd lesions in the skin. In a later work, Sulzberger and Kerr<sup>24</sup> illustrated that hypersensitivity to trichophyton is a "group specific" in human beings and that it occurs exclusively in persons who have or have had tinia infections. Sholtz,<sup>21</sup> as well as Sulzberger<sup>25</sup> found that tests with products of one fungus in this group will give positive results even though the infection has been actually caused by another member of this same group. As an example, a patient suffering from a ringworm infection, from which is cultured *Epidermophyton inguinale*, can react to injections of an extract prepared from *Trichophyton interdigitale*. The same relationship exists between the epidermophytons, trichophytons and microsporons. Sulzberger<sup>25</sup> revealed at this time also that the organisms of the trichophyton group do not react with the monilia group. Only those lesions due to the monilia react to a monilia extract.

In this broad way there is a differential activity in the development of skin sensitization. Patients having fungus lesions develop antibodies present in the circulation which can be demonstrated by their ability to be passively transferred to the skin of normal nonsensitive individuals, thus revealing the existence of specific antibodies or reagins. In a further work, Sulzberger and Lewis<sup>26</sup> illustrated the fact that a trichophyton hypersensitivity can be elicited by means of contact or patch tests using an extract of the fungi.

With this wealth of immunologic evidence bearing upon the close relationship between the sensitivity to fungus extracts in patients having a fungus infection, it is surprising that an immunologic method has not been used more extensively in the treatment of this disease. Attention should be directed to this method of approach, since the "id" lesions often are more serious to the patient than are the primary lesions. The "id" lesion is an allergic manifestation and, therefore, should be prone to more efficient treatment by immunologic methods. It has been common experience that local therapy only aggravates the "id" lesion rather than cures it.

In the ordinary course of events, the development of the "id" might be outlined as follows: From the primary lesions spores are released into the blood stream which travel throughout the body. These spores will reach the skin which has been sensitized; and there, in reaction to the products of the fungi, an eczematoïd lesion develops. The spores lodging in other organs which have not become sensitized cause no lesions apparently. Since sensitization is one of the primary factors in the develop-

TABLE I.

NO.	SEX	AGE	ASSOC. ALLERGY	LESION	DURATION YEARS	IDENTIFIED & CULTURED	SKIN TESTS (SCRATCH)														RESULTS	REMARKS
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ment of the "id," it would seem probable that this chain of events could be made reversible or else broken by means of desensitization.

Sulzberger and Wise<sup>27</sup> have tried desensitization with good results. They treated over 100 cases, although only nineteen are reported, with the conclusion that the longest apparent cures were obtained in treating these fungus lesions with fungus extracts. Robinson and Grauer<sup>20</sup> used autogenous fungus extracts in the treatment of mycotic lesions and had very encouraging results. Schonwald<sup>22</sup> states that, in dermatomycosis, the allergic state is definitely responsible for tissue injury and consequent inflammatory reaction. The ultimate healing is also due to their allergy.

Fungi of the monilia group are strong sensitizers<sup>15</sup> and capable of producing primary skin infections and secondary eczematous eruptions. They resemble closely the trichophyton group. Since a good percentage of fungus infections of the hands and feet are due to the monilia group, and, furthermore, since the trichophytons and the monilias do not interreact, Pennington<sup>19</sup> used separate injections of the trichophyton and monilia extracts in twelve cases with a reported cure of nine, one improved, and no results in two. In another series of twenty-one cases, she attempted hyposensitization with fungus extracts, with the result of curing twelve, improving five, no results in three, and in one a doubtful result. Of 100 reported cases by Van Dyck et al, 81 per cent were improved or cured. Recently, Epstein<sup>9</sup> reported the successful use of fungus extracts in the treatment of dermatologic eczematoid lesions in the aged. His results were obtained using a low concentration (1:10,000 dilution) of a fungus extract given intradermally in doses from .05 to 0.1 c.c. every fifth day. Schonwald<sup>22</sup> also reveals excellent results in the treatment of the trichophytid lesions as well as the primary focus, using low dilutions of fungus extracts. Few investigators report any serious reaction to the use of the fungus extracts. These fungus extracts apparently are very effective in very low dilutions and only small amounts need be given.

Accordingly, with this background, we have attempted to treat a series of epidermophytoses and epidermophytid cases using a fungus extract\* containing the *Trichophyton gypsum*, *Trichophyton interdigitale*, *Epidermophyton inguinale* and *Monilia albicans* in a dilution of 1:5,000. It is quite evident that since all these fungi do not interreact, that a composite mixture had to be made in order to cover the most common causative fungus factors.

#### METHODS AND RESULTS

In Table I, thirty patients are presented who were followed for a period of about a year. All have received previous local therapy. In addition, many had received a course of x-ray treatment. The majority were clinic patients. Ages ranged from three to sixty-three years.

Sex distribution is not particularly significant, since more females, 56.7

\*The Arlington Chemical Co., Yonkers, New York.

# DERMATOPHYTOSIS—JAROS AND KIRSNER

per cent in this series, are seen, generally, in clinic practice. However, the male attendance, 43.3 per cent, is relatively high. This may indicate that the men made a special effort to come in for treatment because of the severity of their lesions.

The average duration of the chief complaint was 4.82 years with a history, in almost all, of a primary ringworm infection of the feet. Dermatophytid lesions appeared universally on the extremities and, in a few, on the face, ears and body.

TABLE II

Epidermophyton .....	5
Trichophyton .....	3
Monilia .....	3
Aspergillus .....	1
Penicillium .....	1
Not Identified .....	1
Positive Cultures .....	14

An associated allergy or history of allergy was found in 56.7 per cent. Of these, almost one half were receiving treatment for their other allergy. The possible effects of such collateral treatment, in this series, is a matter for discussion. It is felt that this point is more of academic interest rather than of practical significance. These patients continued to have the "id" lesions for a long time, and these lesions did not clear even though other allergy was controlled. A clinical impression was gained that, while the skin lesions were clearing up, the present treatment did not contribute to a better control of other allergy, except in a nonspecific way psychologically.

This high incidence of associated allergy is significant in that there is a greater likelihood that sensitization to the offending fungi will occur, and more probably that the persisting skin lesions are also allergic manifestations.

Of the 93.3 per cent skin tested (scratch method), 64.3 per cent were found positive to dry fungus extracts. This high percentage of skin positives is significantly greater than the percentage (56.7 per cent) of previously known allergic persons. This would indicate that a hypersensitivity does develop in persons not known to be allergic. Probably, the percentage of positive reactions would have been higher if intradermal injections of trichophyton extracts were used. The scratch method was chosen because it is deemed expedient, safer, more easily controlled and actually is a more severe criteria of skin sensitivity.

Of the 76.7 per cent cultured, 56.5 per cent were accurately identified as to the causative organism. The lesions selected for culture were from locations which presented the greatest physical disfigurement. This was done purposely for the psychological benefit of the patient whose anxiety was usually fixed on these areas. Cultures were obtained at the time of the initial history and physical examination. Table II reveals the types and incidences of the causative fungi isolated.



Fig. 1. E.P. Upper photo shows extent of granulation tissue and vesicles before treatment. Lower photo shows response after twenty injections



Fig. 2. M.P. Lesions on feet which were part of a generalized distribution



A culture was obtained in the following manner: The lesion was swabbed with alcohol, and a drop of serum from the vesicle or scraping of a licheniform lesion was used to inoculate the culture medium.

In the early portion of this investigation a broth culture medium was used made up as follows:

Water .....	12 liters
Peptone .....	120 grams
Cerelose .....	240 grams
Salt .....	60 grams
Yeast extract .....	12 grams

This medium was chosen because it was used commercially and yielded flourishing growths. However, in this experience, only the bacterial contaminants seemed to multiply. The cases in which this broth medium was used are indicated in Table I as Neg.-b. It is unfortunate that this collateral data was lost because, while waiting for growth and identification of the organism, the patient improved so markedly that subsequent cultures were negative.

In the remaining cases, a standard Sabouraud's agar slant was used. The inoculated culture tubes were allowed to remain at room temperature for two weeks. At the end of this time, there was generally sufficient growth present for identification.

A dilute extract was chosen in order to start desensitization at a low enough level to accommodate even the most sensitive without causing a reaction. It is our clinical judgment that excellent results can be obtained with the use of dilute extracts rather than quickly trying to give the most concentrated extract the patient can tolerate. The immunologic responses can be adequate, and desensitization is accomplished with a therapy employing dilute extracts.

Each patient received a dose of 0.1 c.c. of the extract intradermally twice a week. This schedule was attended by good results. In some patients, the regime was varied slightly as indicated under "Remarks" in Table I. In very sensitive patients, the extract was further diluted, as shown, or a smaller dose given. In those who had improved markedly, the interval between injections was increased to one week, which was usually done at the request of the patient.

In two patients, an attempt was made to increase the dosage in order to shorten the course of therapy. It was found that if more than 0.2 c.c. was injected intradermally, local necrosis would result, with the skin over the wheal sloughing off. This was confirmed many times when sterile saline was injected in equal quantities as a control. Apparently, human skin can accommodate a wheal of 0.2 c.c. as a maximum before the local circulation is disturbed.

No serious reactions were seen after injection, although there were occasional and temporary (a) flaring up of the lesion, (b) local reaction

## DERMATOPHYTOSIS—JAROS AND KIRSNER

at the site of injection associated with a mild lymphadenitis and (c) pruritis.

Generally, pruritis soon disappeared after the initiation of treatment. In the early part of the course of injections, pruritis might return on the day before or the day when another injection was due. In other words, the patients were asymptomatic for a period of three to four days following injection. After a few more injections, pruritis disappears. Occasionally, a patient reveals focal flare-ups in the beginning of treatment, which may be part of a hypersensitivity phase before the desensitization effects take place.

A therapeutic regime consisting of an average of 22.5 injections gave the following results:

Cured .....	40.0%
Marked Improvement .....	43.3%
Improved .....	10.0%
Nonimproved .....	6.7%

These attainments are consistent with those of Van Dyck<sup>28</sup> and Eller<sup>8</sup> wherein 80 per cent or more of patients treated were markedly improved or cured.

Any method of therapy which gives such a high percentage of good effects should be vigorously recommended and adopted.

Any patient who presents himself with a chronic eczematoid lesion, with a history of an associated allergy, who is skin-positive to fungus extracts and from whose lesion a fungus organism can be identified, should receive desensitization as the treatment of choice.

### SUMMARY

Thirty cases of fungus dermatoses are presented, with their relationship to allergy and fungus sensitivity illustrated. Etiologic organisms were cultured and identified. Better than 80 per cent were markedly improved or cured after a desensitization regime using a small intradermal dose of a mixed fungus extract.

Acknowledgment and thanks are offered to Seymour L. Shapiro and Emmanuel Murrow of the Arlington Chemical Co., Biological Laboratories, for their co-operation and assistance in the identification of the fungi cultured.

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## CLINICAL EVALUATION OF NEOHETRAMINE

(Continued from Page 306)

about one and one-half to two hours. He remained free from hives for at least twelve hours after ingestion of each drug.

Five patients were followed for over three months, during which time blood pressure readings, blood counts and urine examinations were taken every two weeks in order to determine any possible ill effect. There were no significant variations in these tests.

(Continued on Page 321)

## PAROXYSMAL DYSPNEA

### Case Report

HARRY S. BERNTON, M.D.

Washington, D. C.

THE patient, M.S.W., was referred to me by Dr. J. R. Jordan of Washington, D. C. A white woman, aged seventy-five, was admitted in September, 1945, with a diagnosis of asthma.

**Family History:** Her father had hay fever. There was no other familial allergy.

**Past History:** At the age of eight or nine, she was confined to bed for eight months with an attack of acute rheumatic fever which affected the heart. Consequently, she was unable to play tennis or dance during her childhood and early womanhood. At the age of sixty-six, cataracts were removed. Six years later, she was hospitalized for two months with "flu" and pleurisy. She had otherwise enjoyed good health during her long life. Her present illness was of four years' duration. The first attack awakened her out of a sound sleep. She was unable to breathe. Her distress was so acute as to necessitate the injection of epinephrine. The attack was accompanied by a generalized eruption of hives of moderate size.

For four years, similar attacks had been of daily occurrence. They usually began at dusk, although they sometimes occurred in the afternoon when she was overtired. Hives had continued to accompany the attacks. An occasional hive, however, had appeared independently of respiratory distress. As many as four attacks had disturbed the sleeping hours. The attacks were perennial and non-seasonal. Vasomotor signs, cough and expectoration were absent. Tightness of chest, slight wheezing, dyspnea and orthopnea comprised the important symptoms. Frequently, she had been obliged to sit up in a chair before an electric fan. She stated, moreover, that the upper portion of her back was very sensitive to touch.

Four years previously, she had consulted an internist and allergist. Tests for protein sensitization had revealed a positive reaction with house dust extract. Aminophylline by mouth, phenobarbital and the continued injection of epinephrine had been prescribed by the consultants.

She remained under observation at the Doctors Hospital from September 17 to 28, 1945. Her temperature ran a normal course. The minimum pulse rate was 68, and the maximum 100 beats per minute. On only three occasions did the pulse rate exceed 90. Respirations averaged 20 per minute. The relevant findings, determined by physical examination, were as follows:

Weight, 100 pounds; height, 61¼ inches.

**Head:** Depression over temporal fossae, indicative of her weight loss of 30 pounds during her illness. **Neck:** Moderate distention of cervical veins. Supraclavicular and suprasternal fossae markedly sunken. **Lungs:** Inspection—expansion equal. Palpation—tactile fremitus normal. Percussion—unsatisfactory. Very light percussion over the back caused wincing. Percussion over the anterior chest elicited a normal note. Auscultation—breath sounds normally vesicular. Rales absent. No respiratory wheeze. Vocal resonance normal. **Cardiovascular system:** Heart normal in size and position. Sounds regular, first sound weak. The pulmonic second accentuated. Harsh loud systolic murmur heard over the precordia. The radial pulses synchronous and equal. All heart beats transmitted. The popliteal and dorsalis pedis pulses palpable. Blood pressure 170/80. **Abdomen:** Slight distention. No masses palpable. Rigidity and tenderness absent. **Extremities:** Edema absent.

Tests for protein sensitization were performed by the cutaneous method with epidermal and miscellaneous proteins, representative pollens, molds, and food pro-

## PAROXYSMAL DYSPNEA

teins with negative results. Intracutaneous testing with the more common allergenic extracts proved negative, also.

*Blood examination*—Hemoglobin, 76 per cent. Red cell count, 4,010,000 per cu. mm. White cell count, 5,900 per cu. mm. Differential count: Neutrophils, 59 per cent; eosinophils, 10 per cent; basophils, 0 per cent; monocytes, 1 per cent, and lymphocytes, 30 per cent. The urinalysis was normal.

The electrocardiographic report is as follows: Rate 92. Regular rhythm, left axis deviation, T waves upright in all leads. P.R. interval, .14 seconds. QRS complexes normal. Impression: Left axis deviation.

Roentgenological examination on the third day following admission showed marked increase in fibrosis throughout both lungs, not inconsistent with the patient's age. There was no evidence of any infiltrative process in the lungs. There was some calcification in the right apex, which was stable in appearance and of no clinical importance. The heart was normal in size and contour. There was no widening of the aortic arch. There was a small calcified plaque in the transverse portion of the arch.

The dorsal spine showed marked productive changes at the anterior margins of the vertebrae and marked thinning of the intervertebral discs. The appearance was that of an osteoarthritis of the hypertrophic type.

On several occasions, a study of the patient was made during an acute attack. She sat upright in her chair. Her expression was anxious. The breath sounds were scarcely audible, interrupted at times by a sigh. Neither the respiratory rate nor pulse rate were accelerated. On auscultation the respiratory murmur was diminished in intensity. No musical râles were heard. Especially noteworthy was the absence of wheezing and noisy breathing and of the intensive pumping effort, characteristic of the acute asthmatic seizure. An injection of epinephrine subcutaneously promptly relieved the distress.

Analysis of the clinical picture was indicated. It will be recalled that the diagnosis on admission was asthma. On the one hand, the positive family history for allergy, the intermittent eruption of hives, the eosinophilia and the favorable response to epinephrine suggested a disturbance allergic in origin. On the other hand, the negative results of the tests for protein sensitization, the roentgenological examination, electrocardiogram and the dyspnea without wheezing were not revealing of the nature of the mechanism involved.

A critical review of the symptomatology was necessary. Shortness of breath would come on at any time during the day and required no medication. Shortness of breath invariably appeared before the completion of dinner at six o'clock, and attacks of dyspnea recurred during the night. She was "afraid to eat and sleep." Of special significance was the patient's statement that she experienced a "clutching feeling in the region below the left breast," after her dinner "has been down only a minute." At times, this region was sensitive to touch.

The advent of symptoms after the large meal of the day, and the "clutching feeling" and tenderness of the anterior lower left chest pointed to an involvement of the upper portion of the digestive tract. The resulting dyspnea after eating suggested an interference with respiration due to external pressure exerted upon the lungs. The tentative diagnosis of a diverticulum of the esophagus in the thoracic portion was justified by anatomic and physiologic considerations.

On September 24, 1945, seven days after admission, the findings of an examination of the digestive tract with bismuth disclosed the following: The esophagus showed deviation towards the right in its lower third. This was due to the presence of a large hiatal hernia of the stomach. Aside from the presence of the hiatal hernia, the stomach was quite normal in appearance. There was no deformity at the pylorus nor of the cap.

With the recognition of the disturbed relationship between the organs of the thorax and of the abdominal cavity—a relationship not entirely unsuspected—the

## PAROXYSMAL DYSPNEA

question of surgical intervention inevitably presented itself. One surgeon of the younger school recommended repair of the hernia. Another surgeon of the older school did not approve of any radical operative procedure because of the advanced years of the patient.

The patient returned home. Suppositories of aminophylline and dilaudid hydrochloride were prescribed to supplement the injections of epinephrine. The ingestion of small frequent meals and the curtailment of starchy foods was likewise recommended.

It is noteworthy that the patient had included a "slight wheezing" in her list of symptoms. Consulting physicians had suggested the diagnosis of asthma. Is it possible that in the case under discussion the asthmatic state is present and is independent of the hiatal hernia?

On repeated examinations, the absence of musical râles and wheezing has been striking—even at the height of an attack of dyspnea. Agreement is universal that, in asthma, spasm of the bronchi is produced by the muscular contraction of their walls. In this connection, the observations of Henry Hyde Salter, made many years ago, remain unchallenged. He states: "We know in health that respiration is noiseless, but that when the breathing becomes asthmatic it is accompanied with a shrill sibilant whistle. We know, too, that hollow tubes give no musical sound, when air rushes through them, if they are of even calibre, but if they are narrowed at certain points, if their calibre is varied, the air in them is thrown into vibrations, and they become musical instruments. The wheezing of asthma, then, is as positive evidence of bronchial contraction as if we could see the points of stricture—it is physical demonstration."

If this criterion be applied to our patient, the diagnosis of asthma cannot be confirmed.

During the four years of incessant attacks, various medicaments had been employed. A total number of thirty-four capsules of Benadryl, in divided doses of 50 mg. each, failed to relieve. The injection of epinephrine had always proved dependable when suffocation threatened. No evidence had thus far been adduced to prove that bronchospasm was primarily the cause of the dyspnea. If, therefore, the surmise be correct that the dyspnea was the direct result of pressure by a distended stomach upon lung tissue, the relief from distress afforded by epinephrine merits an explanation. In the treatment of asthma, epinephrine has ranked first in importance. The stimulation of the terminations of the bronchial sympathetic fibres by epinephrine causes a relaxation of the musculature within the walls of the tubes. Consequently, the bronchi become widely dilated, and a greater volume of air is admitted to the alveoli of the lungs. This pharmacological action takes place in the normal as well as abnormal lung.

It may not be amiss to make inquiry into the causes of diaphragmatic herniation. They are three in number: (1) congenital, (2) traumatic, and (3) acquired. The first two causes can readily be excluded.

Hernias of the acquired type, however, tend to occur in adult life. They are secondary to small defects in the diaphragm and result from strain. It will be recalled that a sudden attack of dyspnea during sleep first signalled the invasion of the thoracic cavity.

Our patient was unaware of any unusual physical strain prior to her present disability. Accordingly, the relaxed state of muscular organs, frequently encountered in very old people, may have been a contributing factor to the formation of a hernia through a weakened or defective diaphragm.

The patient again sought help and consultation in March, 1947, eighteen months after her hospitalization. She was approaching her seventy-seventh birthday. She continued to survive her increasing distress. Her present complaints depicted the underlying pathologic conditions. She felt weaker. The attacks of shortness of breath were more frequent and more severe. More medication was required during the day.

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There was very seldom any distress after breakfast, which consisted of two or three slices of toast, eggs, and two cups of coffee. She ate very little lunch. In the evening, shortness of breath would come on before the end of dinner, accompanied by the "clutching feeling" in the region of the left lower chest. She then required

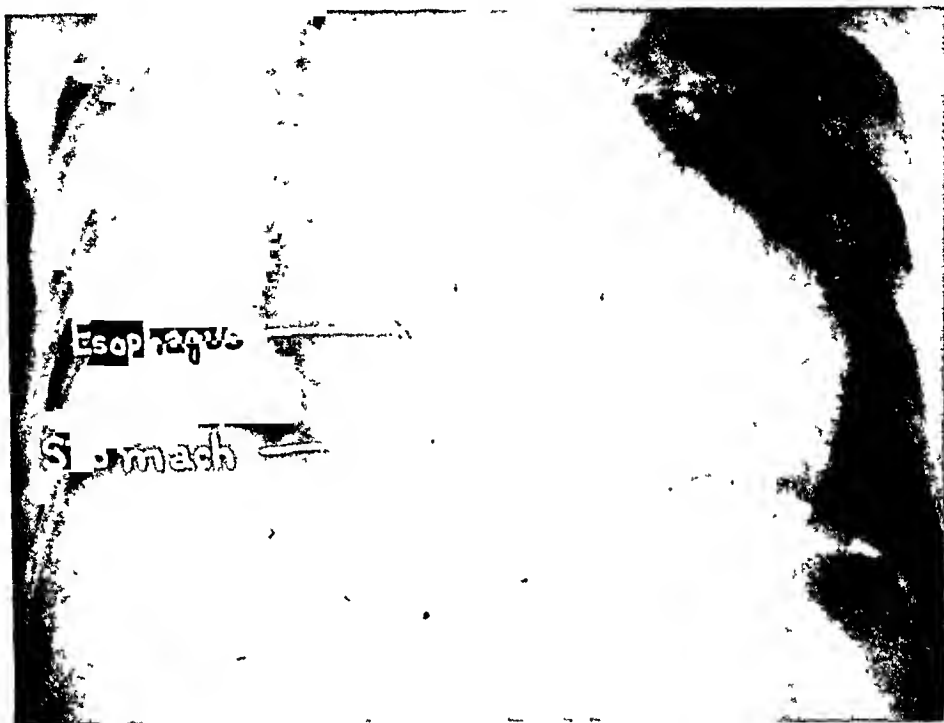


Fig. 1. Radiograph taken on March 20, 1947.

epinephrine immediately. She needed at least four injections of 5 minims of epinephrine daily, followed by a tablet of phenobarbital. After the injection of epinephrine, she experienced some "rumbling" in the abdomen. Eructations were rare. A slight cough usually preceded an attack, and there was practically no expectoration. Hives had been absent for one year. The pain and tenderness which had been confined to the upper dorsal area had become more widespread. At times, the pain was very sharp under the shoulder blades.

The following symptoms assumed significance: (1) During the past several months, when aroused from her sleep by an attack, she had noticed coughing and wheezing—more than ever before. (2) She was experiencing pounding of the heart on occasions.

On physical examination, the area of cardiac dullness was enlarged. The apex measured 4 inches from the midsternal line in the sixth interspace. The systolic murmur was transmitted to the left axilla. The pulse rate varied from 74 to 78. The systolic pressure registered 160 mm.—a slight decrease from the earlier record. Edema of the extremities was absent. When observed during a daytime attack of dyspnea, the patient stated that she felt as if she had been running. The respiratory movement appeared labored and scarcely audible. Musical râles and wheezing were not present.

Five attempts were made to determine her vital capacity. She was most reluctant to take a deep breath and blow into the spirometer. She feared the effort would bring on an attack.

## PAROXYSMAL DYSPNEA

A control roentgenological examination was made on March 20, 1947. The findings were as follows: Examination of the chest showed the following heart measurements: M.R., 5.1 cm.; M.L., 9.7 cm.; total, 14.8 cm.; chest, 23 cm. Hence, the heart was markedly enlarged to the left and to a small extent to the right. There was the usual fibrosis along the bronchial tree which is seen at this age period.

Examination of the upper gastrointestinal tract showed an esophagus which was deviated to the right and entered a large hiatal hernia (Fig. 1). This was approximately 6 cm. in diameter and of about one-third the capacity of the stomach. The esophagus seemed probably shorter than normal but the abnormality of contour was considered due to the hiatal hernia. The diaphragm moved freely. The stomach was otherwise normal in appearance.

A comparative study of the x-ray plates revealed a marked increase in the size of the heart, chiefly of the left side. Cardiac function as evidenced by pulse rate, absence of edema and cyanosis seemed unimpaired. Nevertheless, the nocturnal cough and nocturnal wheezing and occasional pounding of the heart may justify the diagnosis of a cardiac asthma of recent onset.

The movements of the two sides of the diaphragm were studied with the fluoroscope in the late morning before lunch. Their free and equal movements despite the possible embarrassment of the herniated stomach are noteworthy. This observation is of importance in excluding the presence of an intrabronchial growth or foreign body, as an unforeseen complication.

### SUMMARY

A patient, now in her seventy-seventh year, with a diaphragmatic hernia involving about one-third of the capacity of the stomach, has been seeking relief from an allergist because of some allergic implications and complications.

### REFERENCE

1. Salter, Henry Hyde: *On Asthma—Its Pathology and Treatment*. P. 35. London: John Churchill, 1860.

### ACKNOWLEDGMENTS

It is my pleasure to record my thanks to Drs. Arthur C. Christie and Fred O. Coe for their roentgen reports and to Dr. Fred A. J. Geier for his electrocardiographic study.

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## CLINICAL EVALUATION OF NEOHETRAMINE

(Continued from Page 316)

### SUMMARY

Neohetramine, a new antihistaminic drug, was used to treat 279 persons. The results compared favorably with corresponding observations on other antihistaminic drugs. Side effects were rare, but should be reckoned with as in all antihistaminic therapy. The best results were obtained in allergic nasal disease and urticaria.

### REFERENCE

1. Scudi, J. V.; Reinhard, J. F., and Dreyer, N. B.: Pharmacological characteristics of Neohetramine, a new antihistaminic drug. III. *J. Allergy*, 19:184-199, (May) 1948.

10 Peterboro  
Detroit, Michigan

MAY-JUNE, 1948



# Editorial

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*The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.*

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## ON THE EDITING OF PAPERS

The ability to advance knowledge by scientific investigation and the capacity to put the description of the resulting factual material into readable language are not necessarily or universally present in the same individual. Readers of ANNALS OF ALLERGY are invited to take part in a discussion (by letter) concerning the functions of the editors.

On the one hand, should the editors limit themselves to the mere correction of possible factual inaccuracy? To follow this course would result in the publication of some papers, excellent in fact but bad in grammar and worse in style. To quote McDaniel,<sup>+</sup> "His selection of papers, the knowledge that they are factually reliable, his judgment in the matter of accessory material, his taste in the make-up of the journal, should obtain for the editor all the recognition he should properly seek. He is not or should not be a schoolmaster." To this school belong those who believe that if a man is literarily inept, so much the worse for him. Let him appear to his fellows and posterity as he is.

On the other hand, have the editors other duties? As objective arbiters should they not make certain that all the gold has been mined; that the facts have been put forward to their best advantage; that the prolix be made more succinct and the overbrief, more detailed? Are the facts not more important than the man? To present them in their best light acquires for them in their utmost clarity the widest acceptance consistent with the deepest understanding.

In other words, is the man to be respected more than his work or are the facts above the personality? Is it possible to insist that contributions be made concise and clear without fear of offense, or must we tread warily for those who resent the transposition of a comma, however misplaced? Shall we reject papers that are poorly written or shall we accept everything as is, if factually valid?

As the writer of the paper or its reader, which do you prefer? Please tell us.

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<sup>+</sup>McDaniel, W. B.: Letter to the Editor. *Science*, 106:491, 1947.

# Progress in Allergy

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## HAY FEVER

### A Review of the Literature of 1947

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In the last year, some 150 papers dealing with hay fever and related problems appeared in the world's literature. The great bulk of the papers dealt with the new group of chemical compounds which were originally introduced as "antihistaminics" but which we now recognize better-termed as "antiallergics." A year has passed, and a true clinical evaluation of this group of substances is now a part of the literature. Many articles have appeared, dealing with pollen surveys, method of surveys, pollen purity, chemistry, immunology, diagnostic methods, attempts at standardization, therapy including prophylactic, specific and nonspecific methods, all of which will be included in this review. It is with deep regret that the opening statement of our last year's report,<sup>56</sup> which stated that "to the worker in allergic problems, the preparation and standardization of pollen extracts is of prime importance; the lack of uniformity and agreement in these matters is disturbing," is as true today as it was then.

#### BOTANY AND POLLEN SURVEYS

Durham,<sup>25</sup> technical director of the committee of the American Academy of Allergy on national pollen surveys, reported the adoption of a standard factor for volumetric conversion of ragweed gravity slide counts obtained with the standard technique. This factor is equal to 3.6, and is arrived at by averaging the catch of ragweed pollen on one square centimeter of slide exposed in the standard instrument, compared with the average catch per cubic yard of air by a simultaneously operated and independently calibrated volumetric sampler. The sampling apparatus devised by O. C. Durham, is simple, easy to make, and inexpensive when purchased.

This method, accepted by the National Pollen Survey Committee of the American Academy of Allergy, is not the last word for evaluating the quantity of pollen in the air over a twenty-four-hour period, due to the fact that many factors enter into pollen distribution any time during the day and night, as temperature, wind velocity, humidity, and sudden changes in barometric pressure. Durham<sup>25</sup> calls attention to this in his article, in which he discusses spot testing. In summarizing his studies, he states that by the use of the Hill dust pump or his so-called Air Whip, which is a 36-inch aluminum rod for swinging a slide in a circle with the oiled face forward, he is able to make spot tests under variable conditions. He was able to test the allergen-producing ability of sixty plant species and several fungi. As a result of repeated spot testing of the air in the immediate vicinity of small plants, small plots, or extensive acreages, some very striking figures for maximum production have been obtained. With the usual gravity tests, a pollen count of 5,628 per cubic yard of air is recorded against 9,600,000 per cubic yard of air by the spot method. In another test by the routine gravity method, a *hormodendrum* count was recorded as 20,000, compared to 869,000, by the spot method. This report discusses the amount of air contamination under various meteorological conditions, and explains the marked variation in pollen counts as reported by the usual twenty-four-hour average gravity slide method.

## PROGRESS IN ALLERGY

In conjunction with Durham's work, a large number of the allergists<sup>131</sup> located in and around the metropolitan district of New York, undertook a survey of ragweed pollination during the 1946 season. They used the technique recommended by the pollen survey committee of the American Academy of Allergy, staining the slide by the Calherla stain, using a cover slip of 2.2 cubic centimeters square, and counted under low power. The number of granules per square centimeter in twenty-four hours was equal to the number of pollen grains counted, divided by 4.84. The pollen grains per cubic yard was equal to that number times 3.6. In summarizing, they stated that the pollen counts in New York City were rather low in 1946, and the highest counts, in order, were Brooklyn, Flushing, Manhattan, Rockaway, Ozone Park, Queens, Bronx, Staten Island. It was felt that the pollen counts in Manhattan were most representative of the city as a whole. It was also noted that the peak occurred at about the same time in each one of the stations.

A similar survey was carried out by Kailin<sup>54</sup> in the District of Columbia, using the methods described above.

Werner, Reed and Stormfels<sup>134</sup> report a pollen survey conducted in 1945 at Albuquerque, New Mexico. The gravity method of collecting pollen was employed. Stations were set up from 4 to 40 feet above the ground level. Four hay-fever seasons were noted, with the major season extending from April 13 to October 28. The spring season, from February 12 to May 7, produced the highest counts, with Juniper, cottonwood, and Bermuda grass as the prime offenders. The summer season extended from May 7 to August 7, with Bermuda grass, Russian thistle, and plantain in large amounts. The fall season extended to the first week of November, with Russian thistle, pigweed, and false ragweed as the chief offenders. Pollen counts as high as 1,400 were recorded during the spring, with counts below 100 for the summer and fall seasons.

Stroh,<sup>121</sup> in his article on pollens of the Northwest, divided those pollens found east of the Cascade Mountains and those along the coastal region. In the Northwest, there are three pollen seasons: the tree season beginning in March and lasting well into May; the grass season beginning in May and lasting through July; and the weed season beginning sometime early in May, but mostly in June, and lasting well into September. The coastal area contains a greater number of offending pollens than the area east of the Cascade Mountains.

Jennes, in collaboration with the National Pollen Survey Committee of the American Academy of Allergy, using the standard sampling device and the standard method, reports a three-year study carried out in Waterbury, Connecticut. The pollen counts for the three-year study were correlated. None of the counts were very high.

Walton and Dudley,<sup>120</sup> reporting on hay fever in Manitoba, in the *Canadian Medical Association Journal*, state that there are three pollinating seasons. The spring season begins the latter part of April and continues to mid-June, the summer season begins in late May and continues until mid-July; the fall season begins in late July and continues until early September. The spring season is due to the pollens of trees, namely, the poplar, elm, Manitoba maple and oak, willow, birches, and alder. The summer season is due to the pollen of the bluegrass, timothy, June, and redtop grasses. The fall season is due to the weeds, namely, giant, western, and perennial ragweeds, burweed marshelder, Russian thistle, Kochia and sages.

Several reports on pollen surveys from foreign investigators have been reported. David Ordman,<sup>87</sup> discussing pollinosis in South Africa, stated that there are a number of trees, grasses, and weeds that are important. Eighty per cent of all pollen extract preparations are used in the grasslands. In South Africa the season begins in June and lasts until October. The common tree offender is the cypress, although in some areas the pepper tree is important. The common grass is that commonly known as the Cosmos, and of the weeds, those belonging to the Compositae family, and the khaki weed, are most common.

In discussing allergic diseases in Palestine, Lass<sup>61</sup> stated that cases of seasonal hay fever are comparatively few, in contrast to perennial vasomotor rhinitis, the incidence of which is very high. Bermuda grass, which grows perennially, was the chief offender. It was noted that the Palestine atmosphere carries a strong scent of citrus fruits in April and May, and is a known cause of nasal catarrh. He further stated that there have been no exhaustive pollen studies in Palestine similar to those done in the U. S. Although mold extracts are used in testing patients, there has been no systematic survey.

Atmospheric contamination by mold spores has frequently been reported as a factor in producing hay-fever symptoms. *Alternaria* and *hormodendrum* are the two molds which have been chiefly incriminated. Deamer and Graham<sup>21</sup> reporting an atmospheric survey from the San Francisco area, showed that 59.5 per cent of the mold colonies cultivated were due to *hormodendrum*, as compared with 2.4 per cent *alternaria* and 19.2 per cent *penicillium*. It is interesting to note that there was no striking seasonal incidence of mold spores, making the diagnosis of clinical mold sensitivity difficult.

Froughtman<sup>39</sup> reported from Barcelona that *aspergillus*, *penicillium*, *cladosporium*, and *alternaria* were the most important molds noted in his survey. Relatively higher counts were observed in the harbor area of the city.

Nilby,<sup>55</sup> the first to use the Petri method of mold identification in Sweden, conducted his survey from August to December, 1946. The greatest concentration occurred in the last days of August with an increase in misty weather. The concentration was low during the winter, but even in severe cold weather, spores were found in the air. The common outdoor fungi were *penicillium*, *pullularia*, and yeast-like fungi. *Penicillium*, the most common indoor fungus, did not show seasonal fluctuation. Other fungi found in homes were those belonging to the *alternaria* and the *monilia* groups. Exposure of plates in large and small cities, country and rural areas, indicated that the greatest mold concentration occurred in the smaller cities and rural areas. The highest spore counts were noted in barns and threshing mills.

Seltzer,<sup>111</sup> in a paper, "Pollen Counts—Their Proper Place in Hay Fever," discussed the weaknesses of pollen counting and the inaccurate deductions that are drawn from the twenty-four-hour glass slide pollen counting method.

Wallis<sup>125</sup> reported on "Peat, Hayfever and Pharmacognosy." From his studies of pollen granules in geological formations in Great Britain, the clinically effective pollen season runs from early March until late September. This period can be divided into three phases: (1) tree pollen, (2) grasses, (3) dicotyledonous barks.

King and Brooks,<sup>59</sup> in an article on the terminology of pollination, felt that there were four major categories of pollination: (1) within an individual flower, (2) between flowers of the same plant; (3) between flowers of different plants of the same variety (where varieties are recognized) or species; and (4) between flowers which are on plants belonging to different varieties or species.

## IMMUNO CHEMISTRY

Abramson,<sup>1</sup> by means of the moving boundary method of electrophoresis of Tiselius, ultra-centrifuge, precision diffusion techniques, isolated highly purified fractions of pollen extracts, and found that the molecules responsible for clinical pollen hay fever and asthma were not large protein antigens, but ones of comparatively low molecular weight, of the order of 5,000 or less, with chemical properties similar to, but not characteristic of, proteins. Preliminary studies indicate that the pollen extracts are complex mixtures of many components with, however, a main colorless component readily isolated by means of the electrophoretic technique. The main colorless component of giant ragweed has been named Trifidin, that of the dwarf ragweed, Artefolin, and that of timothy extract, Pratensin.

Abramson has introduced a new term in describing these substances, because they have some chemical properties resembling protein; however, they are different from ordinary proteins. The name he has suggested is the term *protoproteins*. A *protoprotein* would be a substance on the border line between the higher molecular weight polypeptides and the low molecular weight proteins. It is hoped that by the use of the methods described above and chemical studies, immunologic data will be more valid, since antigens would be pure and not multiple complexes.

We concur with Abramson when he stated that pollen extracts are not simple antigenic solutions, but complex mixtures containing many components that are biologically active. How then is one justified in insisting that chemical standardization procedures properly assay the biologic activity of pollen extracts? Furthermore, that the protein nitrogen as assayed by the phosphotungstic acid precipitate method represents not only the inactive but the equally active biologic skin fraction. Furthermore, to measure the allergic activity of a pollen extract by only a biologic response like the skin test, using complex mixtures, is also open to scrutiny. The chemical determination of total nitrogen, and the further evaluation by studying its biologic activity, seems to us to be the best method of standardization available to us at the present time. If and when the chemical characterization of the purified fractions can be studied by immunologic methods, the interrelationships between chemical and immunologic activity, as well as ability to produce sensitization and protection, will then lead us to more accurate methods for standardization.

A number of articles dealing with the chemical and immunologic specificity of various fractions from ragweed pollen extract, have been reported this year. Among these studies is the report of Sherman and Stull<sup>113</sup> adding further evidence of the immunologic specificity of fractions 1 and 2. In summarizing their results, they found that the reaction of fraction 1 and fraction 2 of low ragweed pollen, with ragweed-sensitive serum in passive transfer, showed evidence of the independent specificity of the two fractions. With one serum, fraction 1 was 1,000 times as reactive as fraction 2, while with another serum, fraction 2 was 100 times as reactive as fraction 1.

Ragweed-sensitive patients treated with the separate fractions, developed specific antibodies to the fraction injected. Serums of rabbits injected with fraction 1 showed specific reactions with this fraction in precipitin tests, passive sensitization of guinea pigs, and passive sensitization of human skin. Only one of the three rabbits injected with fraction 2 developed precipitins, but these were specific for fraction 2. In both man and rabbits, fraction 1 was a more active antigen than fraction 2. The preparations of fractions 1 and 2 were described in previous papers of these authors.

Baldwin et al.,<sup>4</sup> reporting on their studies of the chemistry and immunology of low ragweed pollen extracts, prepared their fractions by serial alcohol precipitations of aqueous low pollen. This was followed by chloroform treatment, as suggested by Sevag, as a method of separating proteins from carbohydrates. In their discussion, they noted that this work was undertaken with the hope that, in the field of atopic sensitivity, a study of ragweed might reveal some immunologic specificity of the nitrogen, or of the carbohydrate (polysaccharide) fraction, similar to that shown by investigators for bacteria. They compared the immunologic activity of three fractions of low ragweed pollen extract prepared by serial precipitation with alcohol, and treatment with chloroform with that of standard pollen extract. Fraction B contained approximately 7 per cent nitrogen and 14 per cent carbohydrate; fraction D contained approximately 5 per cent nitrogen and 58 per cent carbohydrate, and fraction S contained approximately 1.4 per cent nitrogen and 60 per cent carbohydrate, and gave a negative ninhydrin test. Standard pollen extract and fractions B and D, but not fraction S, were precipitated *in vitro* by rabbit antiragweed serum. Standard pollen extract and fraction B, but not the others, were also pre-

cipitated by rabbit antifracton B serum. No preeipitations were observed with rabbit antifracton D serum. Sensitization of guinea pigs to standard pollen extract was produced with each fraction. Sensitization to fraction B was produced with all fractions except fraction S. Sensitization to fraction D was produced only with fraction D. No sensitization to fraction S could be produced. Studies of untreated ragweed-sensitive persons showed that the threshold of sensitivity, for skin and conjunctiva to standard pollen extract, was lower than to any of the three fractions. Fairly strong evidence was presented, indicating that the carbohydrate fraction of low ragweed pollen extract is not a very active antigen, since, while it sensitized guinea pigs to whole ragweed extract and elicited positive reactions in untreated ragweed-sensitive human beings, it failed to produce precipitins in rabbits. The further the attempts to purify and fractionate the original ragweed pollen extract were carried out, the less striking and consistent were the immunologic reactions observed. Immunologic reactivity diminished with a decrease in the nitrogen content of the fraction.

Stone, Harkavy and Brooks<sup>120</sup> reported their studies on the chemical investigations of giant ragweed pollen. Their method of preparation was, first, defatting giant ragweed, and then extracting with distilled water for twenty-four hours in the refrigerator. Three similar extracts were thus prepared. The extracts were combined and concentrated. The material was then diluted and dialyzed for fourteen days. The dialysates were combined and evaporated. The active material in the dialysates is heat stable, and not denatured at an interface. The dialysate was then precipitated with trichloroacetic acid. The filtrate, after complete precipitation with trichloroacetic acid, was then treated with picric acid, and after complete precipitation, the resulting filtrate was treated with phosphotungstic acid.

In summarizing their results, they stated that when an aqueous extract of defatted giant ragweed pollen was exhaustively dialyzed, about one-half of its allergenic activity appeared in the dialysate. The active principle in the dialysate was heat-stable and not denatured at an interface. The dialysate was further purified by treatment with trichloroacetic acid. After the removal of that precipitant, saturated picric acid was added, and then the excess eliminated. Neither treatment precipitated the active principle, nor was the skin reactivity of the extract appreciably changed. Phosphotungstic acid precipitated the active principle. Upon getting rid of the insoluble addition compound of the phosphotungstic acid, thereby making it soluble again, the activity was recovered. The most highly purified fraction yielded a positive ninhydrin, biuret, and Molisch test.

Stevens<sup>117</sup> studied the quantitative changes in various fractions of the precipitable nitrogen in ragweed extracts during incubation at 37° Centigrade. Their data showed a decrease in the nitrogen precipitated at half and full saturation with sodium sulphate at 37° Centigrade. The phosphotungstic acid precipitate also showed a decrease. The analyses suggest a degradation of protein molecules to split products of lesser magnitude, to a point where they are beyond the level of effective precipitants.

Alexander, Johnson and Bukantz<sup>2</sup> studied thermostable antibody titers as determined by the precipitation methods. They found that there was a general lack of correlation between thermostable antibody as determined by the methods used, and the degree of clinical protection. The mechanism by which clinical improvement occurs following specific pollen therapy, remains unknown.

Brown et al,<sup>14</sup> studying the response of the blocking antibody to oral pollen therapy, showed that there was no correlation between increase in antibody titer to clinical symptomatology, and therefore finally concluded that there was no correlation between skin test, eye test, antibody titer, and clinical results.

Urbach<sup>125</sup> and his associates, in a discussion of the chemical and immunologic basis of oral pollen propeptan therapy in hay fever, gave as evidence of the specificity of their preparation, the fact that it protects a highly sensitized guinea pig against

a multiple lethal dose of pollen antigen. They also showed that the pollen propeptans retain their type-specific immunologic properties when tested by the Prausnitz-Küstner reaction. If animals that had been sensitized to pollen by the oral or bronchial or intravenous route, and had been hyposensitized by pollen propeptans, were then attempted to be shocked by pollen, no reactions occurred, thus indicating protection. The results of these investigations seemed to constitute, to these authors, experimental confirmation of the therapeutic value of specific pollen propetane therapy in hay fever in man.

Swineford, Houlihan, and Robinson,<sup>122</sup> studying antibodies for ragweed extract, could not confirm the observations of Cohen and Weller's preliminary report of the demonstration of precipitins in the sera of treated, and not in untreated, ragweed-sensitive patients. Neither the thermostable antibody nor reagin could be titrated when human sera were mixed with collodion or parlodion or other particles which had been sensitized by ragweed extract. Antiragweed rabbit serum agglutinated ragweed-sensitized collodion and parlodion particles consistently. Normal rabbit serum controls, properly prepared, were negative.

Squier and Lee,<sup>125</sup> in a discussion of the lysis *in vitro* of sensitized leukocytes by ragweed antigen, summarized their results by stating that polymorphonuclear leukocytes obtained from heparinized whole blood of patients sensitive clinically, and by skin tests, to ragweed pollens, were studied, following the addition of short ragweed antigen to the heparinized blood. Lysis *in vitro* of these sensitized leukocytes was evidenced by reduction of approximately 43 per cent of the total number of cells. The disintegration of leukocytes was inhibited by heating for one hour at 56° Centigrade, presumably by inactivating the ragweed-sensitizing antibodies. No significant change in the total number of leukocytes occurred after the addition of ragweed in bloods inactivated by this technique. No significant reduction in the number of leukocytes occurred after the addition of ragweed antigen, in the manner described, to unheated blood samples of ragweed-sensitive patients treated adequately by injections of ragweed antigen.

Miller and Campbell<sup>80</sup> gave a preliminary report on the experimental evidence in support of a new theory of the nature of reagins. Reaginic sera of egg-sensitive patients were added to crystalline ovalbumin in varying dilutions, and incubated at room temperature for two hours. Rabbit antiovalbumin serum was then added, and the mixture incubated at room temperature for two hours, and at 4° Centigrade for forty hours. The precipitate obtained was analyzed for protein by the Folin-Ciocalteu method. It was found that the reaginic sera increased the amount of precipitate. Reaginic serum from pollen-sensitive individuals, employed as a control, failed to produce an increase in the amount of protein precipitated. It was concluded that the reagins in egg-sensitive serum are in some way incorporated in the ovalbumin-rabbit antiovalbumin precipitation.

An interesting paper by Rhoden and Sutherland,<sup>100a</sup> of Australia, on the chemical nature of a protein-free preparation of egg white, linseed, and castor bean, recalls the work of Grove and Coca, Black and Moore, who asserted that the active fraction of pollen is a carbohydrate. After a comprehensive review of the literature on this subject, Newell stated that the general opinion held by most workers was that the active fraction of pollen is a protein. The authors pointed out that it was necessary to mention some of the confusing difficulties met in the past, e.g., some crude allergens possessed several chemically distinct fractions which reacted differently in different allergic persons, all of whom reacted to the unfractionated substances. Some workers ignore the fact that the complete separation of mixtures of large molecules is impossible. Biologic methods may detect traces of proteins which chemical tests would not, and certain proteins are not precipitated by reagents which usually precipitate most proteins—perchloric acid, for instance, is an excellent precipitant for most proteins but will not precipitate ovomucoid. The employment of

enzymes to destroy an ingredient in a mixture, does not remove the last traces; even chemical methods of precipitation are apt to fail in the complete removal of some organic compounds. There is no proof that all pure allergens are antigens, so caution must be used in interpreting the results of experimental sensitization. A sensitizing substance which is related in no way to the allergen may be mixed with the latter. However, these experiments are useful to demonstrate the lack of purity in the supposedly "purified" substances. The skin-reacting substance may be only a part of the allergen occurring in nature. It may resemble the hapten group, yet may not be antigenic until it is combined with a protein or polypeptide. It is possible that eventually it may be shown that there are marked differences in the chemical nature of different allergens. Even prolonged centrifugation may fail to remove very finely divided matter which is capable of producing reactions in very sensitive patients. No simple method is known for determining slight differences in the activity of two extracts of similar antigens.

## STANDARDIZATION

The question of standardization of allergenic extracts has not been clarified to any great extent. It is the opinion of the reviewers that at this time the only workable method involves the use of total nitrogen determination, with additional information from biologic skin testing. Those who have had experience in the chemical determination of total nitrogen know that it is much easier than the accurate determination of protein nitrogen. The type of solution used for the precipitation of substances to be analyzed is very important, and, secondly, the method. In any event, the chemical analysis of the so-called protein nitrogen includes substances that do not fit into the strict definition of complete proteins. The evaluation of standardization by skin testing alone can also lead to much variation. The specifically sensitized skin does not always give equal or equivalent reactions even in the same individual. Suffice it to say that the skin reaction at any dilution of a solution will give only comparative reactions. This is to be expected, since the materials tested are always mixtures of antigens.

Wodehouse,<sup>135</sup> in a series of papers, gives much useful information on this problem. His "cutaneous reaction units" form a simple numerical system of recording reaction intensities in direct skin testing and in passive transfer experiments. Utilizing the formula  $(e - w)w = n$ , where  $e$  equals the over-all diameter of the erythema, and  $w$  the diameter of the wheal,  $n$  represents the number of cutaneous reaction units, which can be expressed by multiplying the wheal diameter by the excess of erythema diameter over that of the wheal diameter in millimeters.

Wodehouse<sup>136</sup> continues with this problem by using the above method of recording, using a standard pollen solution prepared by a standard method and kept under standard conditions. Potency is expressed in terms of standard nitrogen amounts per c.c. Physiologic potency is expressed as the ability to neutralize homologous reagin serum as compared to that of a standard extract. It is then, in turn, expressed in terms of the standard nitrogen units. Using the passive transfer method, as described by Prausnitz-Küstner, the neutralization is carried out *in vivo* or *in vitro*, and expressed in cutaneous reaction units.

Wodehouse,<sup>137</sup> in discussing the neutralization, by passive transfer method, of sera which contain reagins for both timothy and Bermuda grass, noted that one did not completely neutralize the other. This led him to the conclusion that each species of pollen possesses a predominant antigen, and one or more subordinate antigens. This also gives more evidence that the skin test alone is not the answer to standardization of allergenic extracts.



## PROGRESS IN ALLERGY

### POLLEN PURITY

Ellis and Dahl<sup>31</sup> examined 260 different lots of dry pollen purchased from commercial sources: 68.1 per cent were found authentic and uncontaminated, 20 per cent were slightly contaminated, and in 10.4 per cent the contamination was natural in character; 6.5 per cent were incorrectly labelled, and 5.4 per cent were seriously contaminated. They suggest that certification of pollen for extraction should be required. This suggestion has been taken up by the committees on standardization of extracts of both national allergy societies, and with the help of Dr. Veldee of the U. S. Public Health Service, an attempt will be made to bring pollen, for extraction, under certain specific requirements, and be certified as to its purity.

### FUNGI

Morrow<sup>81</sup> correlated the ten most frequently encountered fungi, reported from stations distributed throughout the U. S. They were as follows:

Alternaria	Sterile Mycelia (pale or dark)
Hormodendrum	Torula
Penicillium	Fusarium
Aspergillus	Trichoderma
Pullularia	

The first six varied in amounts at different stations. The occasional type was significant as part of the aerobiological picture of the local region, and may be responsible for a stubborn case of respiratory allergy.

Prince, Tatge and Morrow<sup>81</sup> reported on their further studies on mold extracts prepared by twelve modifications of their original method, using several members of the aspergillus family and alternaria. In the first five modifications in which the pellicle was treated by drying slowly or by lyophilization, and then ground before or after defatting, no significant difference was found in the skin test. Skin-reacting substances were found in the broth and washings. No histamine or histamine-like substance was found which could act as an irritant. In the next four methods, alternaria produced a very strong antigenic substance in the broth, as well as in the pellicle, whether the pellicle was washed, unwashed, defatted, dried slowly, or lyophilized.

In the next four methods, an attempt was made to separate large and small molecular aggregates, by dialysis from the broth and the unwashed pellicles. Even though the separations were not complete, definitely increased skin activity was noted from both the broth and pellicle in that part of the material which remained in the dialyzing membrane (large molecules).

Sellers and McKenzie,<sup>110</sup> in a study of the mold content in the air over a five-year period in the Abilene, Texas, area, showed that on exposed agar plates, molds were present throughout the entire year. In sixty-nine patients with hay fever, and in thirty-one patients with asthma and hay fever, there were sixteen instances of pure mold sensitivity, and eighty-four instances of mixed mold sensitivity. In the younger age group (one to twenty years of age), mold sensitivity particularly was prevalent.

### DUST

In a comprehensive report, the standardization committee of the American College of Allergists<sup>102</sup> reported a co-operative investigation on the preparation and standardization of house dust extracts. Directions for the preparation and analysis of extracts known as crude concentrate, alpha picoline, and absorbed concentrate were given. Cutaneous tests showed definitely no relation to total nitrogen present, and

"some" relation to phosphotungstic-precipitated nitrogen. Successful standardization can be done by a combination of chemical and biologic methods. The chemical method involves the determination of total nitrogen and the total and free alpha amino nitrogen of the phosphotungstic acid precipitate. Such extracts are then tested biologically, and dilutions are made, based upon their chemical analysis, namely, dilution so that the extract contains .003 mg. of phosphotungstic acid precipitated nitrogen per c.c.

Rimington et al,<sup>75,101</sup> reporting their studies on the allergens of house dust, stated that the character of allergic substances obtained from different dusts did not differ materially. Therefore, they use a single dust supply obtained mostly from carpets. They describe their method of preparation, fractionation, concentration, and sterilization. Their material on chemical analysis contained 2 to 3 per cent nitrogen, 20 to 40 per cent hexose, and from 30 to 50 per cent ash. Hydrolysis with acid, yielded a galactose sugar, and some amino acids. Electrophoretic study at pH 8 revealed two main components, one immobile and colorless, the other mobile and colored, having similar chemical composition and equal potency when tested on dust-sensitive patients.

In a further study,<sup>119</sup> in which patients were tested with mold and house dust extracts in a concentration of  $10^{-4}$ , a number found dust-sensitive also showed positive reaction to molds. Of the patients negative to dust, none gave positive reaction to molds. A striking chemical similarity was noted between the three polysaccharide products derived from molds after hydrolysis, and the dust antigen. All exhibited a polypeptide-like grouping of simple amino acids associated with a polysaccharide complex. The usual color reactions for proteins were not obtained.

Continuing their studies on dust antigen,<sup>75</sup> normal and allergic patients were tested in dilutions of the dust antigen  $10^{-4}$ ,  $10^{-5}$ , and  $10^{-6}$  concentrations. In the normal group, 58 per cent were negative to the  $10^{-4}$  dilution, as compared with 10 per cent of the allergic group. Seventy per cent of the allergic patients showed positive reactions in a dilution of  $10^{-5}$ . In forty-five patients who were tested with dust extract  $10^{-5}$  dilution, cat hair, feathers, and mold extracts, thirty-five were positive to dust, and of the thirty-five, twenty-two were found sensitive to one or more of the other allergens used for testing. No patient was found who reacted to one of the other allergens but not to dust. On desensitization treatment, a definite decrease of the threshold reaction was noted, but no blocking antibody was found in the bloods of the patients so treated.

## DIAGNOSIS

Healy<sup>51</sup> described a new type of blood test for allergen diagnosis. Using first serum and later plasma, he found that the addition of either pollen extract or histamine caused a turbidity which could be seen microscopically in many samples, and in higher-dilution by means of the nephelometer in all samples. For extensive testing with a large number of allergens, high dilutions of serum or plasma were necessary to carry out such a program, and modifications were developed which formed the basis of this clinical report. The technique of the procedure was described in detail. During a period of five years, a group of 2,164 patients were studied. Of this group, a positive reaction to histamine was obtained in only 139 patients. Fifty-four other patients who were histamine-sensitive, also reacted to extrinsic factors. Eighty-nine per cent of the first group and 77 per cent of the second had relief of symptoms by treatment with histamine. Among 1,963 patients reacting to extrinsic factors, 1,732 (88 per cent) had satisfactory results.

Brown et al,<sup>13</sup> studying the relationship of dyspnea and diminished vital capacity as a symptom and a sign in hay fever, concluded that many patients with hay fever had a reduction in their vital capacity. In a number of these, there was no correlation between peaks and depression of their vital capacity profile as related to the dates of

pollination of the plants to which they responded with nasal symptoms. None of the patients were wheezing at the time of the determination. In the patients studied over a period of five pollen seasons, there was no apparent correlation between their diminished vital capacity and their prognosis. It was concluded from this study that among those patients in whom there was a diminished vital capacity, the majority did not materially benefit from their treatment, while the majority of those who had no diminution did benefit. Patients with hay fever should be questioned regarding dyspnea, which may be the earliest sign of bronchial involvement and additional proof of pollen sensitivity.

Schiller and Lowell<sup>73,106</sup> studied the effects of drugs in modifying the response to aerosolized pollen extracts, as determined by vital capacity measurements, and concluded that atropine and Pyribenzamine failed to influence pulmonary response to inhaled extracts of pollen. This is a dangerous method, since cough and severe symptoms may follow exposure to the extracts; however, the authors feel that this method is promising, particularly as the lung, the chief site of the disease process, serves as a test organ. This method also afforded an objective test, where in many cases a decrease in vital capacity may occur without the subject's being aware of any reaction.

Samter and Becker<sup>105</sup> reported their studies on the nasal secretions of normal and ragweed-sensitive subjects with marked skin reactivity and circulating reagins, by inserting cotton plugs saturated with 10 per cent sodium chloride solution into the nostril. Passive transfer sites were prepared with 0.1 ml. of a Seitz-filtered secretion, and retested twenty-four hours later with ragweed solution. The nasal secretions in seven of twenty ragweed patients contained ragweed reagins.

Wodehouse<sup>139</sup> called attention to the fact that passive transfer recipients must be carefully chosen, and it is best not to use any individual who has any allergic background. In four patients, skin-test sensitivity to ragweed developed in the course of passive transfer experiments. On questioning, all four patients had atopic backgrounds. None developed clinical hay fever, though adequate exposure was met with in 1947. Generally, it is assumed that it is very difficult to sensitize human beings.

Stier<sup>118</sup> in a general discussion, evaluated allergy testing, its limitations and significance. He concluded his remarks by stating that the degree of skin reaction doesn't necessarily constitute the response of an allergen; neither does the size of the reaction indicate the severity of symptoms that can follow. The tests that gave most of the false positive and negative reactions were foods.

## TREATMENT

The treatment of hay fever usually occupies the greatest amount of attention of the allergist. Therefore, any form of treatment which improves on method of administration, preparation of extracts, adjuvant materials and drugs, which either supplement or complement specific therapy, are important.

With the confusion which exists with the chemistry of pollen, the best extracts available, in the experience of the writers, are the orthodox extracts prepared by the use of aqueous solutions of the whole pollen.

Guerrant and Swineford<sup>47</sup> state that they can control symptoms of active hay fever by injecting dilute extracts co-seasonally. Only suspected pollens are used for skin testing, and suitable mixtures used for each case. Extracts are injected subcutaneously, starting with a dilution which gives a mild intradermal reaction, which may be as dilute as 1 to 500,000 or as strong as 1 to 10,000. Rapidly progressive amounts of extracts are injected once or twice daily, until symptoms abate or local reactions occur. When symptoms abate, tolerated amounts are injected every two or three days. Nonspecific therapy is used as an adjuvant treatment.

Mary Loveless,<sup>70</sup> in an attempt to apply immunologic principles to the treatment of hay fever, reported a method for the management of hay fever by the use of

Freund's adjuvant. Freund's adjuvant utilizes an emulsifying agent, mineral oil, with aqueous antigen and killed acid-fast bacilli, and a lanolin-like substance, Falba or Aquaphor. Loveless hoped to accomplish a booster effect by this method, with increased tolerance and fewer injections. She had some difficulty as she increased the dose with some reactions. However, on the whole, this method gave her thirteen excellent results, as compared to ten in a similar group of thirty patients. This method is reported as a preliminary study, and is not to be construed as a final evaluation of this type of therapy.

Lazarowitz<sup>62</sup> used chilling of the site of antigen injection as a method of therapy in extremely sensitive patients, in order to delay absorption. An ice bag was applied to the mid-outer part of the arm fifteen minutes before and fifteen minutes after injection. Thirty hay fever patients were treated with doses higher than those usually used, with favorable results.

Rackemann<sup>66</sup> discussed the bearing of pollen tolerance in the treatment of hay fever. He said that good results can be obtained with a small series of doses, provided that the amounts of these can be correlated with the tolerance of the individual. He also noted that the level of absolute tolerance appeared to be a fixed point for each patient. Generalized reactions can be minimized if the point of tolerance is recognized, and treatment kept at a lower level. Good records are essential, as the level may vary from year to year.

Koelsche,<sup>60</sup> of Mayo Clinic, in a general discussion of the management of hay fever, includes, besides specific desensitization, drugs for symptomatic relief, hay fever resorts, environmental control, attempts at prevention of pollination of plants, and the avoidance of constitutional reactions.

Bedford,<sup>7</sup> in an article discussing hay fever prophylaxis in the Royal Air Force, stated that in England most of the hay fever therapy is against timothy. He used the scratch tests with a solution containing 20,000 pollen units per c.c. The patients were injected twice a week, increasing the dose by 100 per cent until a reaction occurred. When this occurred, the dose was increased only 85 per cent until another reaction occurred. When the dose level of 50,000 pollen units per c.c. was reached, skin tests were carried out, and if the test was negative, no higher dose was given. However, if the skin test was positive, the dose was increased weekly until a negative skin test was reached. The strength of the solution used was equal to 100,000 pollen units per c.c. Side reactions were few and mild in nature. In one case, the dose level was raised to 260,000 pollen units per c.c. or 2.6 c.c. of the concentrated solution.

Zonis and Rubin<sup>141</sup> attempted to predict the occurrence of constitutional reaction by testing with ragweed pollen fractions. They described their method of preparation and procedure. Their results were not very encouraging, and they felt that this was due to the fact that their method of fractionization by chemical means was not sufficiently accurate to actually separate the proteins.

Rowe and Rowe,<sup>104</sup> discussing the occurrence of allergic symptoms in patients over the age of fifty-five, stressed the fact that seasonal allergy occurred for the first time in thirty-three of 173 patients. These patients required specific treatment, and usually responded with stronger dilutions, in the range of 1 to 500 or 1 to 50 for satisfactory results. Co-seasonal therapy required very weak dilutions in the range of 1 to 5,000,000, or 1 to 5,000,000,000. Prolonged desensitization for months, or for one or more years, was usually necessary.

Fuchs,<sup>40</sup> in a discussion of allergy in geriatrics, said that some patients become allergic for the first time in life at an age past fifty, and that when treated by specific methods, they respond very well.

Oral pollen therapy, using whole pollen as well as pollen propeptanes, appeared again in the literature. Egeberg and Painter<sup>39</sup> reported their results with oral pollen as compared to specific hypsensitization. They concluded that oral pollen therapy

offers a satisfactory method of treatment of seasonal hay fever. They felt that the advantages in this type of therapy were the absence of severe reaction and ease of administration, especially in patients who have had constitutional reactions or those who fear hypodermic medication. The treatment was more readily available for patients who must travel, or cannot come in regularly for parenteral therapy. Desensitization was more rapid. The disadvantages of oral therapy were the greater cost of material, variability of dosage, and difficulty of control, since no rigid plan of dosage was completely satisfactory.

Brown et al.<sup>14</sup> used oral pollen therapy and studied the skin test blocking antibody response. They felt that whereas there was improvement by this method, parenterally treated patients responded much better.

Urbach et al.<sup>125</sup> from their studies on oral pollen propeptane therapy in hay fever, felt that the most successful alternative to subcutaneous hyposensitization with pollen extract was the oral administration of pollen. Crude pollens were likely to cause distressing gastrointestinal symptoms resulting from absorption of the undenatured antigen contained in the pollen. Urbach, in 1931, introduced oral therapy with pollen digests. These were obtained through the digestion of pollen by hydrochloric acid, pepsin, or trypsin. Urbach claimed that this procedure deprived the pollen of their native protein, but not of their type specificity. To the propeptane, the saponin glycyrrhiza was added as an adjuvant. Scientific immunologic data was advanced as added evidence for this method of treatment.

Kaplan et al.<sup>56a</sup> in a controlled experiment using oral whole pollen in children, concluded that oral pollen offered very little as compared to the specific hyposensitization method. When statistics were evaluated in this controlled study, the patients received little, if any, benefit from oral pollen.

Since the advent of the group of drugs classified as antihistaminics which are known to exert antiallergic properties, several studies have appeared in which these agents have been used alone or in conjunction with specific therapy. The studies of Arbesman et al.,<sup>3</sup> Leibowitz et al.,<sup>64</sup> and others, seem to indicate that these drugs will in no way take the place of specific hyposensitization, but merely act as symptomatic agents. In the study of Arbesman, Pyribenzamine alone relieved hay fever symptoms to about the same degree as did the specific hyposensitization therapy, plus symptomatic drugs. This study used the IBM punch cards as a means of studying variables. It is well to note that statistical studies of this type give valuable information, but actually do not give a true clinical evaluation.

A report appeared under foreign letters in the *Journal of the AMA*, from Copenhagen, on hay fever. Brunn and Schwartz<sup>15</sup> treated sixty-nine hay fever sufferers from 1941 to 1945 at Rigshospitals' Polyclinic Allergy Division. Sixty-three of the patients' symptoms occurred during the months of June and July. In this group, fifty-nine had good results by desensitization, which started on April 1 and continued for two months. Twenty-four to thirty injections were given in all. A number of the patients included in this group had seasonal asthma. The results of treatment were disappointing in this group.

In our experience, the patients who have pollen asthma and hay fever seem to get excellent results for the relief of asthmatic symptoms by adequate specific hyposensitization with ragweed extracts.

## NONSPECIFIC HAY FEVER TREATMENT

Little of importance in the nature of nonspecific methods of therapy in hay fever has attracted our attention this year. Vitamin C has its advocates, which become smaller in number each year. Specific urinary proteose, dead for many years, is revived by an investigator who should try proteose peptone solution by injection before ascribing specificity to urinary proteose.

Edmundson<sup>20</sup> has been advocating a solution formally known as Metapollen, now

known as Agenzin, which is a solution of colloidal silver, copper, and zinc. This method is a modification of the old nasal zinc ionization therapy, which was tried by many and finally dropped. His report in the *Medical Record* is enlightening. Good results were reported, except in those cases with nasal polyps, deflected septi, and broken bones obstructing the openings to the sinuses. The excellent results were accomplished by the gradual, progressive method of shrinkage. Edmundson summarized his report by stating, "There is no longer any merit in skin tests or in the determination of the offending allergen. This therapy clears up all of the classes of causation with equal completeness."

We have had no experience with this type of therapy, but on the basis of previous experience with solutions which cauterize nasal mucous membrane, we see no value over the more tried and conservative methods of therapy.

Bartlett<sup>9</sup> recorded his results with "Ethylene Disulphonate In Allergy," a six-year study including some 1,800 cases. Bartlett got excellent results in 412 cases of hay fever, of which 192 were adults and 220 were children. In this group, 193 were completely relieved and 135 partially relieved, with no relief in eighty-four. In 80 per cent of the hay-fever patients on this type of therapy, the results were satisfactory.

Wasson,<sup>132</sup> reporting on her studies with Ethylene Disulphonate over a seven-year period, still feels that it has definite merit. Among her twenty-six cases of hay fever, which were composed of sixteen adults and ten children, there was definite improvement noted in seventeen patients, and failures in nine. In summarizing her results, Wasson stated, "I don't know why Ethylene Disulphonate helps most victims of allergy, any more than I can explain the body chemistry of many other empirically successful and universally accepted pharmaceutical products."

Bodman<sup>10</sup> reported from Britain on his results with Ethylene Disulphonate in 160 patients, and found that of twenty-four cases with hay fever, eleven were completely relieved and four partially relieved, with no relief in nine. In this group, 62 per cent had satisfactory results. In thirty-two cases which showed definite skin tests and were treated with specific desensitization, twenty-three did not respond favorably. In seven persons who had hay fever, four had satisfactory results with Ethylene Disulphonate following specific desensitization.

It was the consensus of many men, who have had ample opportunity to study this problem of Ethylene Disulphonate, that the material has little or no value in the dilutions used,  $10^{-10}$  to  $10^{-20}$ . According to Avogadro's law, in a solution containing molecules dispersed by  $10^{-17}$ , specific reacting substances would be so few that it would be possible that any given small amount would not contain any of the reacting substance.

Mertins<sup>70</sup> reported in the *J.A.M.A.* several cases on the excessive self-medication with Privine Hydrochloride. Severe reactions, with collapse after withdrawal of the drug, were noted. The frequency with which we meet this type of addiction, and the difficulty with which the marked withdrawal symptoms are controlled, behooves us to be wary of the uncontrolled use of this drug.

Bubert and Doenges<sup>12</sup> reported on the use of a new drug, Ethyl-Nor-Epinephrin (Butanefrine), which has some of the general properties of epinephrine, and which can be used to great advantage in allergy, without the severe pressor effects and central nervous system stimulation which so frequently accompanies the use of epinephrine.

The drug Allergosal (Chemtronic Laboratories), which is racemic epinephrine, has not been approved by the Council on Pharmacy and Chemistry,<sup>18</sup> of the A.M.A. The report stated that it was not as effective as ordinary epinephrine, and that epinephrine-fast patients did not obtain relief even by overdosage. The council felt that the unsupervised use of this potent drug was dangerous.

## PROGRESS IN ALLERGY

### MISCELLANEOUS

The *Journal of the American Medical Association*,<sup>92</sup> in the section on queries and notes, had a number of questions asked and answered, dealing with hay fever. The question of ragweeds in Europe was answered as follows: Some members of the ragweed family are present, but in insufficient numbers to produce any appreciable amount of pollen.

The question<sup>94</sup> of whether or not pollen desensitization should be carried out during pregnancy was answered as follows: The slight possibility of miscarriage resulting from severe systemic reaction should not defer from its usage. Rarely, if ever, does severe hay fever bring on the above symptoms. Mothers-to-be should be kept comfortable. In our experience, hay fever desensitization, carried out at a low dose level to give some protection, is a desirable way of treating pregnant women. The precipitate<sup>93</sup> or sediment which is frequently found in vials of hay-fever pollen extract is probably due to some alteration in one of the chemical ingredients, which is sufficient to cause a precipitate, and is thought to belong to the polysaccharide group.

Several other notes appeared in the *J.A.M.A.*<sup>76</sup> which were of interest. An anti-ragweed drive was attempted in some areas in New York City. Large areas were sprayed with chemicals where the ragweed plants grew in abundance, before the pollinating stage. The Department of Sanitation and Parks, co-operating with the Health Department, destroyed over 1,000 acres of ragweed by this method.

Allergenic diagnostic and therapeutic agents have come under a change in the regulations on revision and expansion of biologics. In a publication of Federal Regulations<sup>83</sup> January 21, 1947, which deals with the sale of biologic products for interstate commerce, it was stated that allergenic diagnostic and therapeutic extracts may be prepared only by a licensed laboratory.

For the first time this year, a special session on allergy,<sup>112</sup> was held as part of the American Medical Association annual convention. Several interesting papers on hay fever and related subjects were presented.

A note appeared in the *Journal of the American Medical Association*,<sup>82</sup> which stated that the Marcelle Cosmetic, Inc., of Chicago, gave a grant of \$1,500 to the American College of Allergists, for the standardization of pollen extracts. This work is going to be done under the direction of Morris Scherago, D.V.M., professor and head of the Department of Bacteriology, University of Kentucky.

### THE ANTIHISTAMINIC DRUGS

Again this year the subject receiving the most attention in the literature was the antihistamine drugs. In reviewing this literature, we have roughly classified the reports into those dealing primarily with pharmacology and experimentations, those on clinical results, and those on side effects and reactions.

Although it is not the province of this paper to delve into the minutiae of the pharmacologic and other experimental aspects of the antihistaminics, certain reports are included to indicate the tenor of work being done in this field.

Rose, Feinberg, Friedlaender and Feinberg<sup>103</sup> made a careful study of comparative anaphylactic activity of Benadryl, Pyribenzamine, Antergan and Neoantergan. They studied the protective effects of the drugs against histamine by intravenous injection of histamine fifteen minutes after the animal had received the protective drug intraperitoneally. Under the conditions of the experiment, they found that Neoantergan was twenty-five times more effective in protecting the animal than Benadryl; however, the difference in antihistaminic effect was less marked as the dose of the antagonist was decreased. All of the antihistaminics protected 100 per cent of the sensitized animals against anaphylactic shock. Benadryl and Neoantergan were equally effective in inhibiting the contraction of the sensitized guinea pig intestinal strip, caused by the addition of a specific antigen. Anaphylactic contraction was in-

hibited by a lesser amount of the protective agent than that required for the histamine contraction of the same magnitude. The significance of their data was discussed in detail.

The same authors<sup>38</sup> compared four ethylenediamine derivatives, namely, Antergan, Pyribenzamine, Neoantergan, and Benadryl, in terms of the numbers of lethal doses of histamine, against which protection was obtained by a standard dose of 3 mg. per kg. of the drug administered intraperitoneally fifteen minutes prior to histamine injection. One hundred per cent end points of mortality were used: Benadryl protected against five, Antergan against six, Pyribenzamine against thirty-seven, and Neoantergan against 125 doses. However, preliminary studies did not show a marked difference in the antianaphylactic activity of these compounds, comparable to the above variation in histamine shock.

C. A. Winter<sup>135</sup> tested six compounds for antihistamine potency against intravenous histamine, histamine aerosol, and on intestinal strips against histamine *in vitro*, in guinea pigs. The descending order of potency was as follows: Neoantergan, Pyribenzamine, 3015 R.P., 3277 R.P., Benadryl and Hetramine. The ratio of the toxic dose to the effective dose was highest for Neoantergan. Side reactions, however, were least noticeable with it, and most violent after 3277 R.P.

Hamburger, Halpern, and deBray,<sup>49</sup> participated in research on a new series of synthetic antihistamines, which are all derived from thiodiphenylamine, and presented the results of their pharmacodynamic and clinical experiences. These drugs seemed to have greater antihistaminic properties than Antergan and Neoantergan.

In another report, Halpern<sup>45</sup> stated that these drugs showed marked antihistaminic and antianaphylactic activity, and are known as 3015 R.P. and 3277 R.P. The latter was able to protect guinea pigs against 1,500 lethal doses of histamine, and .1 mg. per kg. was enough to protect these animals against fatal anaphylactic shock. It might be well to mention at this point that Feinberg,<sup>35a</sup> commenting on this drug at a recent meeting of the Chicago Society of Allergy, stated that the amount of the drug necessary to protect against 1,500 lethal doses was so high, that if comparable dosages of some of the other antihistaminics were used, the results would approach this; that although these animals did not die immediately, surprisingly enough, twenty-four hours later, there was considerable mortality due to dissolution of the stomach and resulting peritonitis, due, no doubt, as he suggested, to the fact that there was little or no protection against the action of histamine on gastric secretion. This new chemical series is distinguished by being less toxic, and more active than earlier ones.

Mayer, Brousseau, and Eisman,<sup>76</sup> exposed guinea pigs to Pyribenzamine as a 2 per cent aerosol. This procedure protected them against fifteen lethal doses of histamine injected intracardially. The protection afforded by Pyribenzamine aerosol in actively sensitized guinea pigs was less regular than that in the histamine series. Passively sensitized guinea pigs were better protected than actively sensitized animals. Pyribenzamine did not produce any clinical symptoms or irritations or pathological changes in lungs exposed to this aerosol for one to two hours. It was concluded that the action of Pyribenzamine in counteracting histamine is peripheral. The drug is either selectively fixed within the receptor cells of the lungs or, by direct contact, renders the cell refractory to histamine. The therapeutic use of Pyribenzamine as an aerosol was suggested.

Pharmacodynamic studies of Pyribenzamine by Yonkman, Oppenheimer, Reunick, and Pellet,<sup>140</sup> by *in vitro* experiments with isolated, perfused guinea pig lung, showed that Pyribenzamine effectively antagonized histamine-induced bronchial constriction. There was a diminution of and, in over half the animals, a lack of protection in anaphylaxis. Comparable results were obtained in dogs in anaphylaxis, and it was suggested that factors other than histamine might play a role in anaphylaxis in the dog.



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Campbell, Baronofsky and Good,<sup>16</sup> investigated the effects of Benadryl on anaphylactic and histamine shock in rabbits and guinea pigs, and found that Benadryl protected rabbits against histamine shock, but did not protect against anaphylactic shock in animals actively sensitized to egg white. These experiments seemed to indicate that a substance other than histamine is responsible for anaphylaxis.

Reporting on some experimental and clinical investigations with Antergan and Amidryl (Benadryl), Nexmand and Sylvest<sup>84</sup> found that when these antihistaminics were given in doses of .15 to .3 gm. orally, they could not prevent the appearance or reduce the size of histamine wheals, allergic skin reactions, Prausnitz-Küstner's reactions, and reaction produced by a stinging nettle. On the other hand, the drugs had a favorable effect in two cases of urticaria, one case of prurigo in pregnancy, and two cases of hay fever.

From Sweden, Nilzen<sup>86</sup> found that when Antergan and Antistine were mixed with wheal-producing substances, e.g., histamine, peptone, morphine or atropine, and injected intracutaneously, they reduced the vascular reaction considerably.

Traub, Friedmann and Landstadt<sup>124</sup> described a new method which enables a quantitative appraisal of antihistaminic activity from the suppression of the action of histamine on skin capillaries in the rabbit.

The regular *J.A.M.A.* Moscow correspondent<sup>87</sup> wrote that vitamin A was found to have a clearly determined antihistaminic effect. It is well, at this point, to note that Thienes,<sup>128</sup> commented on the fact that laboratory experiments with antihistamine drugs and clinical experience do not necessarily go hand in hand.

The second year of widespread use of the two most commonly known antihistaminics, Benadryl and Pyribenzamine, has, in general, not materially altered the appraisal of those investigators who reported upon them extensively last year. As Walton et al<sup>139</sup> said, Benadryl and probably the related antihistaminics, as at present known, will be limited in their usefulness. At best they are but symptomatic remedies. Although the immediate toxic effects are rather well known, the remote ones must be carefully considered. Allergy to these drugs is a definite possibility, and should be taken into account. In eighteen cases of seasonal hay fever, he obtained marked relief with Benadryl in sixteen cases, and slight relief in two. Toxic effects were present in fourteen cases.

McGavack, Elias and Boyd,<sup>77</sup> reporting on their clinical experiences with Benadryl, felt that it was an exceedingly potent antihistaminic and antispasmodic drug, which lacks unpleasant cardiovascular and nervous side effects, attendant on the use of sympathomimetic agents. Toxic reactions, while common, rarely preclude its continued use.

Logan's<sup>68</sup> experience of a year with Benadryl, in allergic children, indicated that it was a useful drug in the symptomatic treatment of those patients. It was used in hay fever, asthma, vasomotor rhinitis, and urticaria. In children, he stated, the effective dose depended upon the age of the child and the severity of the condition, the duration of effect, and the frequency of administration. The total daily dose varied from 1 to 12 mg. per kg. Benadryl was best administered when the stomach was empty. No marked ill effects were observed in long courses of administration. The most frequently encountered untoward reactions were drowsiness and vomiting, their incidence being approximately 24 per cent; in one case, hematuria occurred. Eleven of thirteen children with hay fever obtained some benefit. He felt that severe cases would probably respond best to a combination of Benadryl therapy and hyposensitization.

Lockey<sup>66</sup> believes that Benadryl is a very useful addition to our therapeutic armamentarium, especially in acute and chronic urticaria, hay fever, and perennial vasomotor rhinitis. The drug very definitely seems to have a sedative effect; it seems to counteract and neutralize the effect of epinephrine. However, careful allergic

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studies and management with desensitization treatment, if indicated, are still the best procedure. Benadryl should not be used indiscriminately, as it produces serious side reactions. In thirty-two cases of hay fever with no previous treatment, six mild cases were completely relieved; in the other twenty-six, relief obtained varied from 30 to 55 per cent. The amount of relief that they obtained varied directly with the pollen count, and if it was high, the symptoms were more severe. Of forty-four cases previously treated with hyposensitization, nineteen took the drug as an adjuvant to provide symptomatic relief; most of these were relieved. It also appeared that a number of patients seemed to tolerate pollen therapy much better.

Of forty-five cases of hay fever in which Benadryl was used, Farmer and Spick-schen<sup>34</sup> observed good results in twenty-three, fair results in eleven, and poor results in eleven. Approximately one-third of these patients experienced side effects, mainly drowsiness and dizziness. They felt that antihistaminics have a definite place in the armamentarium of allergic diseases.

One hundred and thirty-seven patients were treated with Benadryl by Blumenthal and Rosenberg,<sup>9</sup> who felt that the results obtained in urticaria and hay fever were encouraging. Of twenty-three patients with hay fever, fifteen were greatly relieved, five had moderate relief, and three had none. Several of their patients commented on the fact that there were occasions when they were completely relieved of symptoms, and other occasions when no relief was obtained. These authors felt that tolerance to the drug was not encountered, nor did it lose its efficacy over a long period of time. Barnett et al<sup>5</sup> concluded their observations on a series of patients with allergic symptoms who were on Benadryl medication, and felt that it was a valuable drug in allergy. They suggested that treatment be started with a test dose of 10 mg. per day after supper. They found that patients with low blood pressures did not tolerate large doses at first; that treatment with Benadryl is best started three weeks before the pollen season. In addition to this drug, the patient should receive proper instructions in diet, elimination, rest, and hygiene. In this present report, eight more hay fever patients were added to their previous series, and all except one were adults. The dosage given these patients varied from 50 to 150 mg. per day; untoward symptoms occurred in one case, and this of no importance. They reported that all but one case was improved; however, the extent of "improvement" was not elucidated upon.

At this point it might be well to note that Reinstein and McGavaek<sup>35</sup> reported on their technique for the administration of Benadryl. For all adult patients a schedule was prepared in which the initial dose was 150 mg. of Benadryl daily, gradually increased to 600 mg. daily over a period of ten days. The patients were told to take their medication after each meal and before retiring at night. They were instructed to stop increasing the dose as soon as symptomatic improvement began, and to remain on this effective dose for a period of two weeks; at the end of that time, medication was discontinued. If symptoms recurred, however, the patient resumed treatment. For children a similar schedule was followed, except that the maximum dose was computed on the basis of 2 mg. per pound of body weight. Unless side reactions were severe, the patient was advised to ignore them and to continue his medication as per schedule.

Pennock<sup>36</sup> reviewed the effectiveness of Benadryl in various allergic states. He suggested that in series in which results were poor, doses may have been inadequate. He has noted no addiction, sensitization or serious toxic effects after a year's therapy with Benadryl; there was no cumulative effect or tolerance. Of the author's patients, 57 per cent showed various side reactions; 5 per cent interrupted treatment because of these.

In the *Journal of Pediatrics*, Goldstein<sup>45</sup> reported his results with Benadryl on seventy-one children and eight adults. Seventy-six per cent of all groups had excellent, 10 per cent good, and 6 per cent fair to poor results; 8 per cent had no improvement. Dosage ranged from 50 to 200 mg. in the children; continuous treat-

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ment was given for one week to two months. This therapy allowed the child to be in a pollen-saturated area, and yet be symptom free.

Of sixty-five patients treated with Pyribenzamine by Levin,<sup>65</sup> 41 per cent were improved. Best results occurred in those patients who had seasonal symptoms due to pollens. In eighteen such patients, ten (56 per cent) were improved, and eight (44 per cent) unimproved. Side reactions occurred in about 40 per cent; Levin felt, however, that they were less severe and less frequent than with Benadryl. Clinically, his feelings were that the results he obtained last year with Benadryl were slightly better than with Pyribenzamine.

Leibowitz, Kurtz, and Schwartz<sup>64</sup> had eighty-five patients with ragweed hay fever who received 50 mg. of Pyribenzamine twice a day. Symptomatic relief was obtained in nine of twenty-one patients with Pyribenzamine alone; in thirty-five of forty-seven patients who received Pyribenzamine and ragweed desensitization, and in ten of eighteen patients who received only specific treatment. Twenty-five of sixty-eight patients experienced side reactions such as sleepiness, palpitation, nervousness, headache, nausea, dizziness, and dryness of the mouth. The authors stressed the fact that this study was done in 1946, when the pollen count in New York City was exceptionally low.

Henderson and Rose<sup>53</sup> administered Pyribenzamine in an average daily dose of 200 mg. to 138 patients with various allergic complaints. The most favorable results were obtained in a group of sixty-one hay-fever victims, forty-seven of whom were benefited. Wheal reactions to scratch tests with ragweed pollen were diminished by 50 mg. of Pyribenzamine, given an hour prior to testing. Side reactions, consisting of sleepiness, nervousness, nausea, dryness of the mouth, dizziness, insomnia, headache, and vomiting, were encountered. In only two instances, was it necessary to discontinue the medication.

Fuchs, Schulman, and Strauss<sup>41</sup> found from their clinical studies with Pyribenzamine in hay fever that temporary symptomatic relief was afforded. However, it did not immunize or protect the hay-fever patient from the effects of the antigen-antibody reaction for any length of time. The mode of action of Pyribenzamine and similar drugs is still unknown. They feel that there is no definite proof which predicates that all allergic manifestations are the result of histamine activity. Pyribenzamine administered prior to the injection of pollen extract made possible greater dosage increases of the pollen extract, and the patients were able to reach a maximum dosage almost twice the amount they usually tolerated when taking the pollen extract alone. In the letters of the International Correspondence Society of Allergists, Green<sup>46</sup> stated that he similarly found that Pyribenzamine had proven to be of aid when administered prior to pollen therapy in hypersensitive patients, permitting the administration of larger amounts of antigen. He found 25 mg. to be effective, and observed no delayed local or constitutional reactions when the Pyribenzamine had been dissipated.

Feinberg and Friedlaender<sup>36</sup> found Pyribenzamine to be an effective palliative drug in the treatment of hay fever. Side effects were frequently encountered, but were usually mild in character. Engelsher<sup>32</sup> studied the effect of the antihistamine drugs, Benadryl and Pyribenzamine, on simple, multiple and mixed forms of asthma and hay fever in 193 patients he had known for a number of years. These patients were given the two drugs for a three-day trial. In 127 cases, the symptoms were either unrelieved or aggravated; the drying effect resulted in cough and asthma in some patients who never before had had chest symptoms. Of the remaining one-third, some were definitely improved, and others somewhat better. He felt that when these antihistamine drugs are compared with the standard pharmacetic preparations used in various synergistic combinations, such as ephedrine, epinephrine, aminophylline, phenobarbital, iodides and others, the new drugs fail by far in effectiveness in allergic conditions of the respiratory tract. Although the antihistamine drugs may be

of fair to striking value in a small percentage of cases of hay fever and asthma, the vast majority of patients were not benefited.

Bernstein, Rose, and Feinberg<sup>7a</sup> reported that Pyribenzamine gave symptomatic relief in 82 per cent of cases with seasonal hay fever. In a smaller series, Benadryl helped 52 per cent, and Neoantergan, 65 per cent. In fifty-two patients with seasonal and nonseasonal allergic rhinitis who received both Pyribenzamine and Benadryl at different times, and in forty-four patients who received both Pyribenzamine and Neoantergan, they found that the results indicated a more favorable response to Pyribenzamine. In general, the severe hay-fever cases, or those not receiving pollen hyposensitization, did not show as much improvement as the others. The sneezing responded more favorably than the blocking; the incidence of side reactions in the entire series was 50 per cent for Benadryl, 27 per cent for Neoantergan, and 23 per cent for Pyribenzamine. They felt that these drugs are palliative remedies and are not effective in all allergic manifestations, nor in all stages of any one of them. They cannot be considered as substitutes for allergic management, such as desensitizations or elimination of allergens. It is interesting to note, that this work was done in the 1946 season which was relatively mild.

Arbesman et al.<sup>3</sup> conducted a comparative study of Pyribenzamine versus specific hyposensitization in the treatment of pollinosis, and found that Pyribenzamine plus adequate injection therapy gave relief of symptoms in 95 per cent of 242 private patients suffering from ragweed hay fever. In clinic patients, Pyribenzamine alone relieved hay fever symptoms to about the same degree as did the specific hyposensitization therapy plus symptomatic drugs. On the other hand, injection therapy plus the usual symptomatic drugs was more superior in alleviating bronchial symptoms than was Pyribenzamine alone. Pyribenzamine alone, in sufficient dosage, may control the symptoms of seasonal allergic rhinitis to a great degree, but cannot give as adequate relief as does adequate hyposensitization treatment plus Pyribenzamine. The incidence of side effects from this drug was small when given with specific hyposensitization therapy, because smaller doses were required to control the symptoms.

A compound known as "01013," similar to Pyribenzamine, was studied by Lee et al.<sup>63</sup> Twenty-nine hay fever sufferers were given this drug in the fall of 1946, and, in a majority of them, symptoms were relieved. Pierce and Mothersill<sup>88</sup> reported on the same drug, which chemically is N, N-dimethyl-N'-(2-thenyl)-N'-(2-pyridyl)-ethylene diamine. The medication exhibited its greatest effectiveness in rhinitis due to pollen sensitivity, acute urticaria, and histamine-induced headache. The effective dosage ranged from 50 to 400 mg. daily. Twenty-one ragweed hay fever cases were reported; of these, fifteen had complete relief of symptoms, three moderate relief, and three no relief. Five of these twenty-one patients exhibited side effects-of headache, dizziness, depression or lightheadedness.

Again this year there were several reports published on the use of histamine azoprotein. Hebal, Cooke and Downing<sup>52</sup> were not able to raise the "ceiling" dosage of ragweed extract in six of eight patients with the additional treatment of histamine azoprotein. In five patients with ragweed hay fever who had never been treated before, there appeared to be no clinical benefit resulting from treatment with histamine azoprotein. Skin tests with histamine dilutions, and histamine response by subcutaneous injections, were the same before and after treatment. In no patient were precipitins specific for the histamine radicle demonstrable after histamine azoprotein injections, nor did they give protection against constitutional reactions, or protection against clinical allergy of hay fever types.

Dundy, Zohn and Chobot<sup>24</sup> treated twenty children and twenty adults with this preparation; of this group with various allergic complaints, ten had allergic rhinitis. They failed to find any appreciable change in the whealing response of the skin to histamine following treatment; clinically, of the group that had allergic rhinitis, two showed slight improvement. They felt that treatment with histamine azoprotein was

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generally ineffective in their series. Cohen and Friedman<sup>17</sup> feel that a condition like hay fever, in which the exposure to the exciting allergen is maximal, cannot be prevented by treatment with histamine azoprotein. They concluded that it was of distinct value in urticaria and certain cases of bronchial asthma.

The Committee on Pharmaceuticals and Medicaments<sup>99</sup> of the American Academy of Allergy reported on the use of Anthallan and Pyribenzamine. Ninety-eight cases of ragweed hay fever were placed on Anthallan, and only 3 per cent benefited. In twenty-one cases of perennial allergic rhinitis, only 4 per cent received any benefit. Sixty-five per cent of those with hay fever that were given Pyribenzamine were benefited. The opinion of certain observers was that Pyribenzamine was quite capable of controlling the symptoms of hay fever without additional therapy. They note that it is important to remember, however, in the consideration of any of these figures, that the year 1946 was characterized by a relatively low pollen count, and it is highly problematic as to whether statistics obtained that year will apply at a time when the concentration of pollen in the air is very much greater. Certain side effects were noted in about 30 per cent of the cases, but in no instance were these of a serious nature. They felt that although it was not a cure for allergic diseases, it was an important adjuvant in the management of allergic diseases. Wagner<sup>126</sup> used Benadryl or Pyribenzamine in thirty-eight cases of hay fever, and in twenty-four (63 per cent) complete relief was obtained. Three patients derived partial relief, and eleven had none. In forty-four patients under hyposensitization treatment for hay fever but experiencing symptoms during the hay-fever season, the drugs afforded relief in thirty-eight cases. Side reactions occurred in 52 per cent of all their cases. A poor initial tolerance was frequently overcome, by decreasing the dosage for a short period of time, and then reverting to a higher dosage level.

Loveless<sup>69-71</sup> summarized the literature published on therapeutic and side effects of Pyribenzamine and Benadryl, and added 200 cases of her own. In comparing related data for Pyribenzamine and Benadryl, she felt that there was little difference in the efficiency of the two drugs. Side effects occurred more often after the administration of Benadryl than of Pyribenzamine; the ratio was approximately 3:1. A detailed listing of side reactions was included.

Reynolds' and Horton's<sup>100</sup> observations on the use of Thephorin, a new antihistamine agent, indicate that it is a useful drug in the treatment of certain types of clinical problems in which the etiological factor is probably the release of "H" substances. Since only a limited number of patients were studied, definite conclusions were not drawn. The outstanding advantages of this agent were the small dosage required for the control of symptoms, and the uniform absence of toxic manifestations. Animal studies have demonstrated the antagonism of this substance to histamine. In twenty-two cases of hay fever, seventeen had excellent results, four got 50 per cent relief, and one had no relief. It was their impression that the seventeen patients had moderately severe hay fever, while the four with 50 per cent relief had severe symptoms, and were relieved only very early in the season. One patient complained of drowsiness.

We<sup>57</sup> have conducted, and are still conducting, more extensive studies on this drug than these authors, and a preliminary evaluation of our results seems to corroborate these investigators' findings, namely, that small dosages are adequate, and there appears to be a uniform absence of toxic effects. However, when toxic effects are observed, they are usually of a stimulating character.

Schwartz et al<sup>107</sup> treated nineteen cases of hay fever with Antergan, and found that this compound was without definite effect in any case. Side effects, consisting of gastrointestinal disturbances, dizziness, et cetera, occurred frequently.

Kallos<sup>55</sup> felt that Antistine was a very valuable drug in the symptomatic treatment of certain allergic disorders, e.g., allergic dermatoses, serum disease, Ménière's syndrome, Horton's syndrome and certain cases of seasonal and perennial allergic

rhinitis. Antistine was of definite value for the prophylactic treatment of systemic reactions following skin testing and specific desensitization. In therapeutic doses of 100 mg. six times daily by mouth, and/or 100 mg. intravenously or intracutaneously, it did not seem to have any unfavorable side effects, although used over a long period of time (as long as eight months), and it was not habit forming.

The propensity of the antihistaminics for causing frequent side reactions, more or less mild in nature, is well known; however, it would be well to note some of the more unusual and more dangerous side effects that have been reported.

Weil<sup>133</sup> reported a three-and-one-half-year-old boy who was given two 50 mg. doses of Benadryl for the relief of hay fever symptoms. Six hours later a third dose of 100 mg. was administered, and twenty minutes later the child was found sitting up in bed, singing and laughing. There were muscular twitchings of the face, and involuntary spastic movements of the extremities. This was followed by urinary incontinence, and in a few minutes the child was irrational. The speech became slurred, and exaggerated patellar and triceps reflexes were noted. The child slept fitfully for several hours after administration of a sedative. On examination the next day, the child appeared normal, with no memory of the preceding night's events. Following this episode, the child tolerated Benadryl without apparent side effects.

An unusual reaction following Benadryl administration was noted by Geiger et al.<sup>42</sup> After 300 mg. of this drug had been taken over a period of three days, a twenty-six-year-old white woman complained of palpitation, diminished vision, malaise, drowsiness, heartburn, and nausea. Following the next regular dose of 50 mg., the patient was found unconscious. She responded to epinephrine, and three hours later had recovered completely. Seven days following the above episode, treatment with Benadryl was resumed. Once more, after 300 mg. had been taken over a period of three days, the patient complained of the same symptoms as previously mentioned; the drug was then discontinued, and the patient rapidly returned to normal.

Borman<sup>11</sup> noted the danger of self-medication with Benadryl, and illustrated with a case of an eighteen-year-old girl. Two 50 mg. capsules per day were prescribed for the treatment of hay fever and asthma. Excellent relief was obtained the first day, and the patient was encouraged to increase the dose herself. During the following three days, forty capsules (2,000 mg.) were ingested. She became drowsy and irrational, her temperature, pulse, respiration, and blood pressure were normal. She was treated by forced fluids, especially strong coffee, and in forty-eight hours, recovery was complete. He notes that the patient's judgment may have been affected by the first two capsules of Benadryl, thus accounting for the unusual number subsequently taken.

Schwartzberg<sup>109</sup> and Willerson<sup>108</sup> reported that Benadryl, taken in 50 mg. doses two to three times a day by a thirty-eight-year-old white man for the relief of hay fever, caused moderate drowsiness during the first week of its use. During the second week, the patient noted puffiness of the eyes and an increased number of bowel movements. In the third week a feeling of tightness in the arms, forearms, and hands developed, together with numbness and tingling of the hands, drowsiness and mental sluggishness. The drug was then discontinued, and slow improvement followed. After three months, minimal symptoms remained. Most of the above complaints appeared to be an intensification of some of the usual side effects of Benadryl. Neuritic symptoms have been produced in dogs by intravenous injections of Benadryl.

Duerfeldt<sup>23</sup> noted in *Northwestern Medicine* that a teen-age girl took thirty capsules of 50 mg. of Benadryl with a successful suicidal intent. Another patient, a sixty-five-year-old asthmatic, misunderstood directions and took fifty of the 50 mg. capsules at one dose and survived. He believes that all patients on this drug should be warned of its dangers. Sternberg<sup>116</sup> had a patient with hay fever who

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was given 200 mg. of Benadryl daily for about one week, and suffered only slight side reactions. When the dosage was increased to 350 mg. a day, she developed hysteria of a severe grade. After withdrawal of the drug, she became normal within forty-eight hours. Gelfand<sup>43</sup> broaches the possibility of a transient hypertension, resulting from Benadryl therapy in a hay-fever patient, citing two cases in addition to his. Davidson<sup>20</sup> noted the fact that the taking of Benadryl interfered with skin testing.

Blanton and Owens<sup>5</sup> reported an interesting case of granulocytopenia, due possibly to Pyribenzamine. A seventy-four-year-old woman developed fever and marked depression of granulocytes in the peripheral blood after eight weeks of moderate doses of Pyribenzamine. Withdrawal of the drug and administration of penicillin resulted in recovery. The white cell count had dropped from 8,600 with 55 per cent neutrophils, to 1,300 with 3 per cent neutrophils.

Harris and Shurc<sup>50</sup> presented a case of an eczematoid eruption, resulting from the ingestion of Pyribenzamine, and felt that this case fulfilled the criteria of an allergic reaction, because (1) it followed a suitable period of sensitization; (2) readministration after all lesions had cleared up produced an accelerated reaction (reappearance of the dermatitis within six hours); (3) the dermatitis could be reproduced at will by subsequent administration of the tablet; and (4) the reaction resulting from the ingestion of Pyribenzamine tablets was entirely independent of the chemical and pharmacodynamic properties of Pyribenzamine.

Epstein<sup>33</sup> also reported the occurrence of eruptions in two patients while taking Pyribenzamine. One eruption was of the eczematoid type, the other resembled pityriasis rosea. Both cases cleared with discontinuance of the drug, and recurred on its readministration.

Kern<sup>58</sup> had an interesting case, a patient who had taken one tablet of Pyribenzamine after dinner, and subsequently fainted and remained unconscious for several minutes. The following morning she took another tablet after breakfast, and soon after she became very weak. A third tablet was taken after lunch; she became weak again and fainted once more. The patient was prostrated all afternoon and evening, recovered by the next day.

In the Letters of the International Correspondence Society of Allergists, Crandall<sup>19</sup> noted that in a period of several months he had four or five patients who had been taking large doses of either Benadryl or Pyribenzamine and had become very anemic. Their red cell count had gone down to 2.5 to 3 million, and their white cell count ranged from 1,200 to 1,500, with a preponderance of lymphocytes and a breakdown of the red cells. One patient, a physician, died from a blood dyscrasia, after being on a long course of Pyribenzamine. It is Crandall's feeling that there is a definite danger of blood dyscrasia, and that patients taking large doses over any extended period of time should be kept under close observation, taking frequent complete blood counts.

Glaser<sup>44</sup> confirmed the observation, made last year by Hal Davison, that in some mothers, Benadryl and Pyribenzamine greatly diminished the fetal movements. However, he had never seen any newborn infants who had any trouble attributable to the fact that the mothers had been given these drugs while pregnant.

An editorial<sup>27</sup> appeared in *ANNALS OF ALLERGY* on the antihistaminics, stating that previous comments in that organ had emphasized the fact that drugs classified as antihistaminics, such as Benadryl and Pyribenzamine, have profound hypnotic effects. The clinical results, therefore, are not unequivocal as far as their antihistaminic action is concerned. Much data indicates that the use of these drugs as antihistaminics may well be justified, where it is quite certain that histamine is the causative agent. However, in many allergic reactions, such as pollen asthma, the use of Benadryl or Pyribenzamine must be on a different basis. If it is desired to employ these drugs for their hypnotic action, we should certainly do so. We

must understand, however, that we are not using the drugs as antihistaminics, but as hypnotics.

In the *J.A.M.A.*, Waldbott<sup>127</sup> presented a critical inventory of the value of antihistamine drugs. He stated that in hay fever, these drugs are most beneficial in the early part of the season when the sinuses and the nasal mucosa secrete clear, watery fluid, and when there is no evidence of secondary infection. He discussed the side effects, and made mention of the possibility of the development of sensitization to these therapeutic agents. Logan<sup>67</sup> stated that it is well to emphasize that the use of these drugs in the control or prevention of the allergic reaction is not a substitute for thorough investigation of the allergy in question. Commenting further, he stated that if a favorable effect from these drugs is to occur, it is prompt, and rarely does one have to wait longer than an hour to observe it. The duration of the effect has varied from ninety minutes to nearly twenty-four hours. His experience in children has been that side reactions occurred in 25 to 30 per cent of the cases, and in 10 to 15 per cent were sufficiently severe to necessitate discontinuance. He doesn't feel that these drugs are designed for an indefinite period of administration. They found that many children suffering from hay fever received considerable symptomatic benefit from the use of Benadryl or Pyribenzamine. Among patients whose symptoms were severe or complicated by much asthma, the use of these two drugs was not a substitute for a program of hyposensitization with the pollen antigens responsible for the hay fever. They were useful to complement a program of hyposensitization which was giving the patient inadequate relief. He felt the dosage must be adjusted from day to day, because of the variance in pollen counts.

Wagner<sup>126</sup> feels that, from a clinical standpoint, the value of the antihistaminic drugs appears at present to be in the field affording temporary symptomatic relief to certain of the allergic manifestations; their significance in diagnosis and other aspects of the allergic state must await further studies. Meanwhile, they can only be considered as new drugs of certain value, but with troublesome side reactions which often limit their use. An editorialist<sup>28</sup> in *California Medicine* felt that the antihistaminic drugs have a field of usefulness, but that we should not allow them to throw us into the path of "drug store" medicine. The editorial further felt that though our failures for successful treatment in many patients with allergic problems were discouraging, the basic principle, to treat the cause rather than symptoms, still held.

Bret Ratner<sup>97</sup> arrived at the conclusion that the release of histamine has not yet proved to be the fundamental factor in anaphylaxis or allergic reactions; hence, any therapy based on such a concept must be called into question. He felt that Benadryl and Pyribenzamine and other drugs of this group have not been proved to be antihistaminic, either chemically or pharmacologically. These drugs have not proved of value in eradicating allergic syndromes. They do not appear to prevent the entrance of antigen into the circulation and the antigen-antibody reaction. It is the nature of the allergic episode to be self-limited, and it is often spontaneously terminated; for this reason, a wide variety of drugs seem to relieve it. The greatest benefits from Benadryl and Pyribenzamine are derived in acute urticaria and hay fever. These drugs must be used vigilantly, because they have serious side effects. They deserve a place as symptomatic remedies, but this author deplored the fact that some physicians and particularly the lay public felt that they were cures.

## NEW BOOKS

Books dealing specifically with hay fever are lacking this year. Several books in English and in Spanish have appeared, in which the subject of hay fever was discussed.



## PROGRESS IN ALLERGY

Sterling<sup>148</sup> has set forth his experiences and suggestions in the treatment of hay fever. Alexander's<sup>142</sup> second edition of *Synopsis on Allergy* is an improved edition on the original manuscript, but is so brief that unless one has complete understanding of the subject, it is best to use a more comprehensive volume. *Office Immunology* by Sulzberger and Baer<sup>140</sup> contains much information, and is a valuable asset to anyone practicing allergy. Cohen's<sup>144</sup> English volume on allergy has been translated into Spanish, and a number of original volumes on allergy in Spanish and other foreign languages have appeared, namely, those of H. Braga,<sup>143</sup> Lunedei,<sup>145</sup> G. Ruiz Moreno,<sup>146</sup> R. Segre,<sup>147</sup> and A. Zironi.<sup>150</sup>

### REVIEWS

The authors<sup>56</sup> of this present review reported in this journal a similar article covering the literature on hay fever for 1946. The only other comprehensive review of hay fever appeared in the *Archives of Otolaryngology* by MacQuiddy and King.<sup>74</sup> Their article is a comprehensive review of allergy, especially related to the respiratory tract.

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### 1947 NEW BOOKS

142. Alexander, H. L.: *Synopsis of Allergy*. Second ed.
143. Braga, H.: *Contribuição ao estudo da alergia infratuberculínica na infância*.
144. Cohen, M. B.: *Manual de alergia para el medico general*.
145. Lunedei: *Malattie Allergiche*.
146. Ruiz Moreno, G.: *Asma; Alergia*.
147. Segre, R., and others: *Terapèutica clinica III (2a parte) oídos, nariz y garganta alergia*.
148. Sterling, A., and Hollender, H. S.: *Clinical Allergy*.
149. Sulzberger, M. B., and Baer, R.: *Office Immunology*.
150. Zirone, A.: *Allergia nei tumori*.

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### HOTEL RESERVATION CARDS

All members planning to attend the Fall Graduate Instructional Course in Allergy to be conducted by the College under the auspices of the College of Medicine, University of Oregon, November 8-12, please write to the Secretary, 423 La Salle Medical Building, Minneapolis 2, Minnesota, for a stamped hotel reservation card. These cards will be sent to you stating the hotel rates, etc., of the headquarters hotel, the Hotel Heathman, Portland, Oregon. When filling out this card be sure to state the time of your arrival and expected departure.

# News Items

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## AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

The American Society of Ophthalmologic and Otolaryngologic Allergy has officially accepted membership in the International Association of Allergists.

Officers of this Society are: W. Byron Black, M.D., Kansas City, Missouri, President; Kenneth L. Craft, M.D., Indianapolis, Indiana, Vice President; and Francis L. McGannon, Lakewood, Ohio, Secretary-Treasurer. Members of the Council are: Aubrey G. Rawlins, M.D.; French K. Hansel, M.D.; Howard P. House, M.D.; William D. Gill, M.D.; William H. Evans, M.D.; Albert D. Ruedemann, M.D.; Rea E. Ashley, M.D.; and G. E. Shambaugh, M.D.

French K. Hansel, M.D., is a member of the Executive Committee of the International Association of Allergists and is one of the members of the Editorial Board of the new *International Archives of Allergy and Applied Immunology*. The S. Karger Medical Publishers of Basel, Switzerland, propose to issue the journal in the very near future.

## FRENCH PHYSICIANS AWARDED FELLOWSHIPS IN ALLERGY

Two French physicians have been awarded fellowships to take a twelve-month postgraduate course in allergy which will be offered next fall by the University of Illinois' colleges of medicine and pharmacy. The physicians are Dr. Jean Dausset and Dr. Claude Lapresle, both of Paris.

They were recommended for the fellowships by Dr. Hugues Gounelle, a consultant for American Aid to France, and Dr. Andre Lichtwitz, chairman of a military-medical mission to the U. S. in 1945. At that time, Dr. Lichtwitz designated the University of Illinois as the college to train French physicians in allergy.

Eight American physicians also will be selected for the course, starting September 27. The 1948-49 course will be the fourth to be offered by the University of Illinois Allergy Unit.

## NEW PROFESSIONAL TRAINING OPPORTUNITIES OFFERED ARMY DOCTORS

A revised and greatly expanded professional training program for regular Army and Reserve Medical Officers has been announced by Major General Raymond W. Bliss, Surgeon General of the Army. In line with the policy of providing in the U. S. Army the highest standard of medical care in the world, the program calls for 1900 new doctors in the Regular Army and an increasing number of volunteer Reserve officers on active duty. The program is designed to give many more Army doctors the training needed to meet the requirements for certification by the American Specialty Boards, and to further integrate civilian and military medicine. The new program will facilitate the classification and career management system already in practice in the Medical Corps whereby every effort is made to assign professional officers to posts where they can practice in their special fields of interest.

## CALIFORNIA SOCIETY OF ALLERGY

An Allergy Section of the California Medical Association, known as the California Society of Allergy, held its organizational meeting at the Palace Hotel in San Francisco on April 11, 1948. Thirty allergists from the State of California were present. Dr. Willard S. Small was elected temporary chairman and Dr. Frank G. Crandall, Jr., temporary secretary.

Based upon the recommendations of the Nominating Committee, the following

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officers were elected: George Piness, M.D., President; Albert H. Rowe, M.D., Vice President; Frank G. Crandall, Jr., M.D., Secretary, and Milton M. Hartman, M.D., Treasurer.

Based upon the recommendations of the Nominating Committee, the following Executive Council was elected: Giacomo R. Ancona, M.D., George Gray, M.D., George F. Harsh, M.D., Samuel H. Hurwitz, M.D., Hyman Miller, M.D., and Willard S. Small, M.D.

Dr. George Piness, chairman of the combined committee of the American Academy of Allergy and the American College of Allergists, gave a report on the progress of his committee for the establishment of an independent American Board of Allergy before the Advisory Board of Medical Specialties of the American Medical Association.

This new Allergy Section will hold its meetings in conjunction with the California Medical Association each year and will have a scientific meeting with the annual election of officers at that time. Other meetings may be called at that time if deemed necessary. All physicians in the State of California, who are interested in allergy, will be invited to attend these meetings.

The office of the Secretary, Dr. Frank G. Crandall, Jr., is Suite 210, 3875 Wilshire Blvd., Los Angeles 5, California.

### CONNECTICUT ALLERGY SOCIETY

The recently organized Connecticut Allergy Society held its first meeting on Thursday, May 19, 1948, at Fairfield, Connecticut, in conjunction with the annual meeting of the Connecticut State Medical Society. During the business session a Constitution was read and adopted and the following slate of officers was elected: President—S. W. Jenness, Waterbury; Vice President—Barnett P. Freedman, New Haven; Secretary-Treasurer—Russell Welbber, Waterbury; Executive Committee—A. F. Roche, Hartford, and Vincent P. Cenci, Hartford.

A round-table discussion took place on "The Anti-histaminics" which stimulated considerable exchange of views. The meeting was very well attended and gave promise for the success of the group.

---

Mr. and Mrs. Alfred S. Woititz, formerly of Almay, Inc., have organized the Ethix Corporation, bringing to it their wide experience in the field of hypo-allergenic cosmetics and dermatological preparations.

Ethix Corporation is initiating a series of distinguished formulas—each one supplying a specific need, all of them together forming a complete and integrated line of hypo-allergenic cosmetics and dermatological preparations.

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Lonis Schwartz, M.D., formerly Chief, Section of Dermatology, U. S. Public Health Service, announces the opening of his office, 915 19th Street N. W., Washington 6, D. C., Suite 713.

---

Jack Cohn, M.D., announces the association of Gardner S. Stout, M.D., in the practice of allergy, at 450 Sutter Street, San Francisco 8, California.

---

Meryl M. Fenton, M.D., announces the removal of his offices to the Marygrove Medical Center, 8830 W. McNichols Road at Kentucky, Detroit 21, Michigan.

---

John H. Mitchell, M.D., announces the opening of his offices at 695 Bryden Road, Columbus, Ohio.

---

M. Scherago, D.V.M., was elected president of the Kentucky Academy of Science in April, 1948.

# BOOK REVIEWS

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THE 1947 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. 604 pages, 13 chapters, 71 figures. Price \$3.75. Chicago: The Year Book Publishers, 1947.

Many articles on the significant advances in the fields of dermatology and syphilology furnish the latest diagnostic and therapeutic procedures in cases most frequently encountered in these fields of practice. The editors endeavor to discuss and correct common misconceptions regarding dermatology held by many of the laity, nondermatologic physicians and even some dermatologists. Many of these misconceptions are due to the deplorable lack of proper facilities for teaching and research in this country as compared to the European countries.

Treatment and prevention (excluding venereal diseases) is comprehensively discussed. Details of x-ray and other physical therapy, drug eruptions (allergic and nonallergic), miscellaneous hematogenous and other dermatoses, cancers, precancerous and other tumors, mycosis fungoides, leukemia, fungus infections, infestations, venereal diseases (excluding gonorrhea), venereal diseases other than syphilis and gonorrhea, as well as investigative studies, are fully discussed. The various skin manifestations of allergy make this compact year book essential to the allergist. The paper stock, illustrations and print are of the first grade.

F. W. W.

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## RH FACTOR IN IMMUNOLOGICAL REACTIONS

*(Continued from Page 304)*

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64 Rutland Road,  
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\*Levin, S. J., and Moss, S. S.: Clinical Results with Hydryllin in Asthma and Hay Fever, to be published.





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Theophylline Sodium Acetate	3 grains
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Phenobarbital Sodium	$\frac{1}{2}$ grain

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Write for descriptive literature and professional samples.



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# Welcome to Portland!

Portland, Oregon, will welcome the American College of Allergists November 4 to 8, 1948. Here the instructional course of the College will have an inspiring setting, as the "City of Roses" is famed for beauty and hospitality. Portland is one of America's most interesting cities; though 100 miles inland from the Pacific, commerce of the world clears over Portland docks on the Willamette and Columbia Rivers. In tonnage handled, Portland claims to be the second ranking Pacific Coast seaport. Its industries hum with production of raw materials and manufacturing; they include lumber, wool, fishing, shipbuilding, grain, livestock, fruit.

Portland has fifty-six parks, seventeen always-green golf courses, and nearby are great forests, orchards, mountain resorts, ocean beaches. The magnificent Columbia River Highway leads from Portland along the bluffs and through the canyons of the river. Bonneville Dam supplies 3,500,000 horse power to this area, nurturing industries. Timberline Lodge on snowy Mt. Hood is a mecca for skiers. When you come to Portland, be sure to stay long enough to see the sights and enjoy the recreational pleasures.

Delegates to the American College of Allergists will largely travel on the North Coast Limited direct to Portland. This streamlined train, with the newest of Pullmans, has roomettes, duplex roomettes, bedrooms and compartments, and, in addition to its luxury accommodations, serves the "Great Big Baked Potato" meals, so famous with experienced travelers, who know their dining cars. Northern Pacific Railroad trips to Portland will show us 1,000 miles of scenic mountain country, including the following sights on the way, which will be seen at the daylight hours shown:

## *First Day*

- 9:05 A.M.—Falls of St. Anthony on the Mississippi.
- 1:15 P.M.—Detroit Lakes, typical of the 10,000.
- 2:30 P.M.—Red River Valley, "breadbasket of the world."
- 7:15 P.M.—The capitol of North Dakota, then the Missouri River, the Sioux Indian country and the Bad Lands.

## *Second Day*

- 7:00 A.M.—Magnificent Crazy Mountains, north of tracks.
- 8:00 A.M.—Absaraka Mountains; Yellowstone River.
- 8:30 A.M.—Scenic Bozeman Pass and west of Bozeman the junction of Madison, Jefferson and Gallatin Rivers to form the Missouri. The beautiful Gallatin and Jefferson Valleys.
- 11:00 A.M.—Continental Divide of Rockies, 6,356 feet.
- 12:15 P.M.—Butte, "biggest mining camp on earth."
- 3:00 P.M.—Hell Gate Canyon. For 199 miles, train follows the Upper Columbia River (the Missoula and Clark's Fork).
- 4:00 P.M.—Mission Range, most beautiful in America.
- 6:00 P.M.—Cabinet Gorge.
- 7:00 P.M.—Lake Pend O'Reille, Idaho.

## *Third Day*

Prior to arrival in Portland at 7:35 A.M., train passes Bonneville Dam (cost \$31,000,000), Cape Horn, crosses the Columbia River at Vancouver at 7:05 A.M., on a bridge 2,806 feet long, then the Oregon Slough, 1,526 feet, and crosses the Willamette River, 1,769 feet. On clear days Mt. Helens, 9,671 feet, can be sometimes seen.

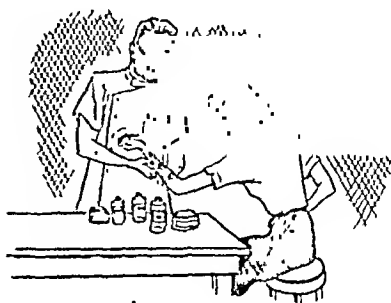
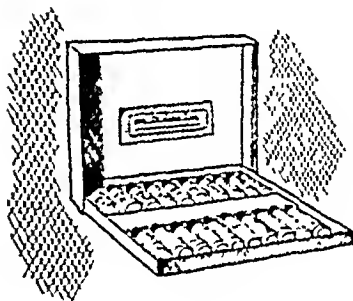
For this trip to Portland, write the National Secretary for Northern Pacific reservations, or call Northern Pacific office if shown in your local phone book. The party will be traveling together.



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3) Modification of formulae, when possible, to eliminate ingredients to which patient demonstrated a sensitivity. (We extend this service to our patrons without extra charge.)



4) Final check tests with modified formulae to make certain there is no reaction.

Preparations by Luzier are regularly available in an unscented variation. They do not contain orris root or rice starch. Any of their normally harmless constituents, however, is potentially allergenic, for which reason we suggest testing, when practicable. Fees for such tests are patient's responsibility.

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**... in the antihistamine  
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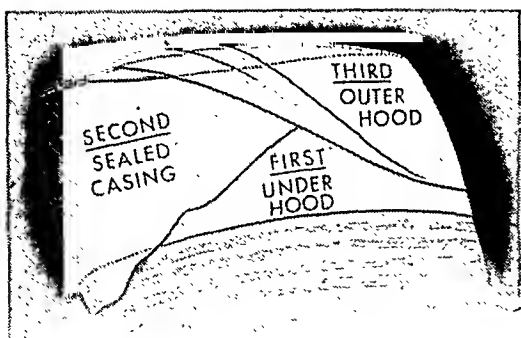


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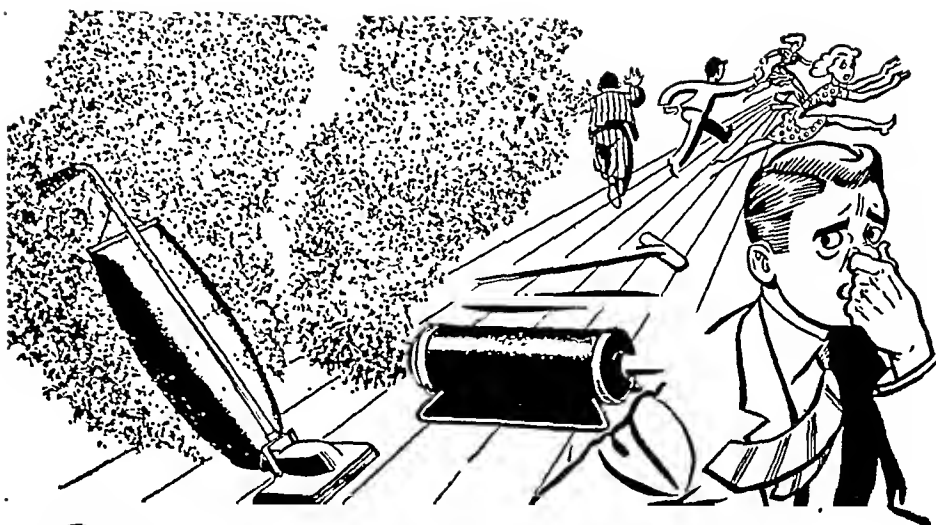
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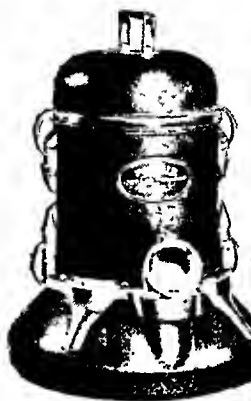
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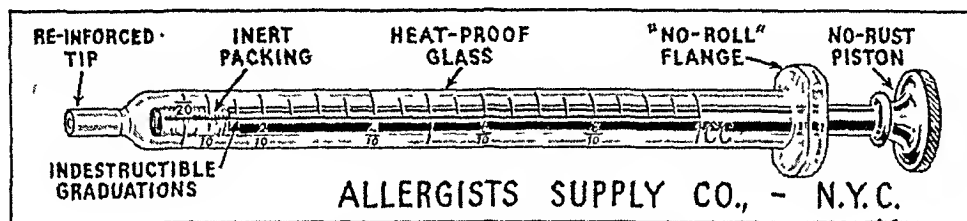
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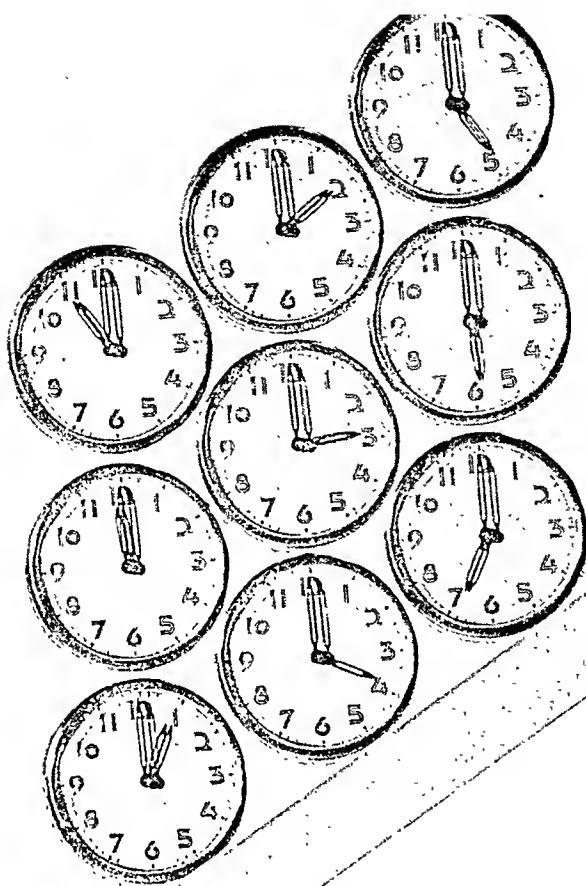
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*Annals of Allergy* is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, a current bibliography, editorials, case reports, new suggestions, questions and answers, news items and matters concerning the affairs of the American College of Allergists.

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man's  
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Number 1

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## THE CLINICAL EVALUATION OF A NEW HISTAMINE ANTAGONIST "DECAPRYN"

ETHAN ALLAN BROWN, M.D., F.A.C.A., L. ROBERT WEISS, M.D., F.A.C.A., and  
JOSEPH P. MAHER, M.D., F.A.C.A. (Assoc.)  
Boston, Massachusetts

THE present report is concerned with a pharmacological description and clinical evaluation of a new histamine antagonist, Decapryn, which has the chemical name 2-[ $\alpha$ -2(dimethylaminoethoxy)- $\alpha$ -methylbenzyl]-pyridine succinate.

### PHARMACOLOGICAL STUDIES

Extensive pharmacological studies on Decapryn have been reported by Brown and Werner.<sup>1</sup> They found the intravenous LD<sub>50</sub> to be 50 to 60 mg./kg. for mice and rabbits. Subcutaneously in mice and rats and orally in mice, the new compound was roughly one-eighth as toxic as when given intravenously. It was approximately one-fifth as toxic orally in rabbits. Studies in male and female mice and rats indicated acute toxicity was similar for the two sexes.

The new antihistaminic drug was found to have a potent and long action in antagonizing lethal effects of intravenously administered histamine in guinea pigs and to possess a wide margin between effective and lethal doses in this species. Doses of 8 to 32 mg./kg. intravenously protected on the average against 133 to 200 LD<sub>100</sub>'s of histamine and in some individual animals protection was afforded against 320 lethal doses.

Doses of 32 mg./kg. intravenously antagonized four lethal doses of histamine four hours later, and a similar dose subcutaneously antagonized nine lethal doses of histamine six hours later. A dose of 80 mg./kg. orally still afforded protection against seven lethal doses of histamine ten hours after administration.

---

<sup>1</sup>Decapryn R was developed in the Research Laboratories of the Wm. S. Merrell Company, Cincinnati, Ohio.

A favorable ratio of activity to toxicity was indicated by the determination that minimal effective doses were less than 0.5 mg./kg. intravenously and subcutaneously and 10 mg./kg. orally, while lethal doses were approximately 64 mg./kg. intravenously, 128 mg./kg. subcutaneously, and 640 mg./kg. orally.

The administration of small doses of Decapryn intravenously completely blocked the depressor response of 1 to 4 mcg./kg. of histamine diphosphate in anesthetized cats. Similar doses in anesthetized rabbits completely blocked the typical pressor effects of histamine, indicating that the histamine antagonist effectively antagonizes both arteriolar constriction in rabbits and vascular dilatation in cats.

The effect of Decapryn on the histamine whealing response was investigated in rabbits, and it was found that single and oral doses afforded long protection for this type of antagonism. Doses of 75 mg./kg. completely inhibited the histamine whealing reaction for six hours and partially inhibited it for over eight hours. A smaller dose of 40 mg./kg. partially inhibited whealing for four to six hours and completely inhibited it for one hour.

The succinate salt did not produce corneal anesthesia in rabbits, even in 4 per cent concentration. This was demonstrated to be a matter of penetration of the salt, since alkaline solutions containing the free base produced deep corneal anesthesia.

Decapryn was found to possess a mild antiacetylcholine action. It was nonirritating to rabbit cornea in concentrations up to 4 per cent, and it produced no local tissue damage following subcutaneous and intramuscular injections of 1 per cent aqueous solutions. Three and one-half per cent solutions produced irritation and necrosis following subcutaneous and intramuscular administration. Intravenous injections of doses up to 8 mg./kg. into anesthetized cats, with a reasonably slow rate of injection, produced only slight temporary pressor or depressor effects. Doses of 2 and 4 mg./kg. produced a similar effect when injected rapidly, and the rapid injection of 8 mg./kg. consistently produced a fall in blood pressure which was of short duration.

Brown and Werner<sup>2</sup> have also investigated effects of Decapryn in certain natural and acquired hypersensitivities in laboratory animals. They found that intraperitoneally administered doses of 2 to 4 mg./kg. reduced anaphylactic deaths, in guinea pigs passively sensitized to beef serum, from eight out of nine for controls to three out of seventeen for treated animals.

The new antihistaminic drug was demonstrated to be highly effective in preventing the edema which follows intraperitoneal administration of eggwhite into rats. Twenty out of twenty untreated animals developed a massive edema of the face and paws one and one-half hours after eggwhite administration. At the same time period, massive edema was present in

only two out of twenty-five animals protected with 150 mg./kg. of Decapryn. However, effects of the eggwhite apparently outlasted effects of the single dose of Decapryn, since the incidence of severe edema was similar for both the treated and untreated groups three and one-half hours after administration of the eggwhite. Repeated administration of the antihistaminic agent prevented the development of edema at any time in a large majority of the tested animals.

Experimental dermal sensitizations were developed in guinea pigs by intradermal injection or topical application of chemical antigens known to cause contact dermatitis. Topical applications of Decapryn base in ointment form reduced the severity of lesions resulting from challenging doses of the antigens.

Repeated oral administrations of comparatively large doses of the new antihistamine compound also reduced the severity of lesions and, in addition, markedly reduced the incidence of severe reactions. Smaller doses of Decapryn also gave protection against challenging injections of the chemical antigens, but they were less effective than the larger doses.

The acute toxicity of Decapryn was investigated in animals by Thompson and Werner<sup>3</sup> preliminary to trial of the substance in man. This work was done in dogs, rats, and monkeys.

It was found that oral doses of 7.5 mg./kg. three times daily produced no evidence of toxicity in dogs. Repeated administration of 15 mg./kg. three times daily caused some loss of appetite and weight, mydriasis, apprehension, and muscular tremors in three out of four dogs. None of the doses employed caused hematologic changes or histologic changes in various internal organs.

The apprehension and other toxic signs observed in the three dogs also occurred in one of two monkeys at dose levels of 16 to 20 mg./kg. three times daily. Lower doses produced no toxic effects in either of the two monkeys studied. None of the doses produced blood dyscrasias or visceral damage as determined by peritoneoscopic examination and histologic study of liver biopsy specimens.

The administration of doses as high as 45 mg./kg. twice daily for a period of thirty-eight days had no significant effect on rats, as judged by gross signs of toxicity, hematologic determinations, and histopathology. Repeated administration of increasing doses from 50 to 150 mg./kg. also had no gross toxic effects. However, an increase of 200 mg./kg. resulted in a decrease in the rate of growth in some animals, and an increase to 400 mg./kg. generally caused decreased food consumption and caused one death.

Repeated administrations of Decapryn to rats, in large doses for a comparatively long period, did not lead to tolerance or accumulation; and repeated doses resulted in toxicity only when these doses approached acutely lethal ones.



TABLE I. 123\* PATIENTS TREATED WITH DECAPRYN

Diagnosis	Number	Clinical Response			Reactions		
		Excellent	Moderate	Negligible	Slight	Moderate	Severe
Bronchial Asthma	41	8	19	14	7	3	3
✓ Allergic Coryza	40	29	9	2	4	6	1
✓ Urticaria	8	7	0	1	2	0	0
✓ Angioneurotic Edema	8	7	1	0	1	0	0
Vasomotor Coryza	7	3	2	2	2	2	1
Atopic Eczema	6	1	3	2	0	0	0
✓ Infectious Coryza	2	2	0	0	0	0	0
— Migraine	1	1	0	0	0	0	0
Generalized Pruritus	4	2	1	1	0	0	0
Erythema Multiforme	3	1	1	1	0	0	0
Contact Dermatitis	2	0	0	2	0	0	0
— Prurigo	1	1	0	0	0	0	0
Total	123	62	36	25	16	11	5

\*17 patients had mixed or multiple syndromes which did not lend themselves to this tabular analysis.

#### CLINICAL STUDIES

For clinical evaluation, 140 consecutive patients (both new and old) were studied in private practice and in two public clinics. The difference in response to medication between private and public clinic patients is well known. The groups, therefore, will be discussed separately. This report is limited to the results seen in the symptomatic treatment of seventy-one private and sixty-nine clinic patients studied in typical allergy practice, requiring relief of their chief presenting symptoms.

*Dosage and Evaluation of Effect.*—We used dosages from 6.25 to 150 mg. four times daily, the latter being employed chiefly in toxicity determinations and in an attempt to evaluate the drug in bronchial asthma, a condition in which antihistaminic agents are, in general, ineffective. Previous studies of antihistaminic agents indicated that the therapeutic dosage was based on the 50 mg. level. However, in view of the pharmacological reports of the comparatively high potency of oral administration of Decapryn, we were prompted to use lower dosage in humans. We found that the usual average dose was 12.5 or 25 mg. In some, the 50 mg. dose was desirable.

The patients were not told that a new drug was being used and were given no information as to the possible pharmacological action or side reactions.

Effects are described as excellent when such relief was so evident that the patient requested the same medication on the next visit. Moderate relief is designated when the patient had some relief, but would be satisfied with more, different or supplementary medication. Negligible relief indicated that no obvious relief was evident.

Side actions are listed as slight, moderate or severe. Of all patients, fifteen had previously taken Benadryl, seventeen had taken Pyribenzamine and sixteen had had both drugs, under the authors' supervision.

*Private Patients (71).*—Bronchial asthma: In this group the highest doses were used, and consequently the highest incidence of reactions was observed. Of thirty-one patients, results were classed as excellent in seven, moderate in fifteen and negligible in nine. Side actions (chiefly drowsiness) were classified as slight in five, moderate in three and severe in two.

Hay fever (allergic coryza): In fourteen patients, excellent relief was obtained in eleven, moderate in three, with slight reactions in one. In five patients with urticaria, four were completely relieved, and there was one who was not relieved with Decapryn, Benadryl or Pyribenzamine. One patient experienced drowsiness. Of four patients with angioeurotic edema, three were completely relieved and (1) moderately relieved. One reported drowsiness. In two patients with atopic eczema, one was relieved completely, the other not relieved.

In two patients with infectious coryza, immediate relief was obtained in both cases. Generalized pruritus was relieved in one-half the patients. Migraine in one patient was completely relieved, and there was significant relief in erythema multiforme and vasomotor coryza.

Multiple or mixed syndromes were observed in eight patients. In six with bronchial asthma and allergic coryza, four were relieved of nasal symptoms, with no effect on the asthma. One was relieved of the allergic, but not the infectious symptoms of the nose. In two patients with bronchial asthma with associated nasal and cutaneous symptoms, the latter two symptoms were completely relieved and there was a slight or moderate effect on the wheezing. There were no side reactions in any of these patients.

*Clinic Patients (69).*—Bronchial asthma: In this group of ten patients, relief was classed as excellent in one, moderate in four and negligible in five. Again, as in the private patient group, there was a fairly high incidence of side actions due to the high dosage employed. Two experienced mild side actions, and one had severe side actions.

Hay fever (allergic coryza): In twenty-six patients, excellent relief was obtained in eighteen, moderate relief in six and negligible relief in two. Reactions were slight in three, moderate in six, and severe in one. As to three patients with urticaria, all were completely relieved, and there was a slight drowsiness in one. Four patients with angioneurotic edema were completely relieved, with no side actions. Of four patients with atopic eczema, three were moderately relieved and one noticed no relief. There were no side actions in this latter group.

Of six patients with vasomotor coryza, two were completely relieved, two experienced moderate relief, and two were not relieved. Side actions in this group were slight in two, moderate in two and severe in one. Generalized pruritus was relieved in one-half the patients. There was significant relief in erythema multiforme and no relief in two patients with contact

dermatitis (poison ivy). There was complete relief in one case of prurigo and temporary relief in one case of migraine.

Multiple or mixed syndromes comprised nine patients in the clinic group. In six patients with bronchial asthma and allergic coryza, excellent results were obtained in both nasal and bronchial symptoms in two, excellent results as to the nose alone in one, moderate relief of the nasal symptoms in two and of the asthmatic symptoms in one. Negligible results were shown in three, moderate drowsiness in one and severe drowsiness in another.

#### SUMMARY

Approximately 80 per cent of all allergic symptoms were relieved by Decapryn. Analysis of results showed that 80 per cent of patients with typical hay fever and over 85 per cent of patients with urticaria or angio-neurotic edema were completely relieved.

In bronchial asthma, the effects, as with other antihistaminic drugs, are quite unpredictable. Of fifty-four patients, 30 per cent were markedly relieved, 40 per cent were moderately relieved, and in the remainder there was no noticeable relief, although in the group with associated nasal symptoms, a good number were relieved of these latter symptoms.

As to side actions, drowsiness was the most commonly encountered and was observed in about one patient out of six. Of the total number of twenty-three patients reporting disturbing side actions, fifteen were in the asthma group which received comparatively excessive dosage. Reactions in the remaining eight patients were moderate in five and severe in three.

On the basis of a dose of 12.5 to 25 mg., used in treating patients other than the asthmatics, reactions occur much less frequently, probably in fewer than 10 per cent of the treated patients.

Of the patients who had previously taken other antihistaminic agents, one preferred Benadryl, three Pyribenzamine, and of the remainder all but one (who was relieved by none) preferred Decapryn, which, on the basis of these clinical studies, appears to be a valuable addition to the antihistaminic or antiallergic agents now available for the management of allergic conditions.

Further studies on the effects of Decapryn on cutaneous whealing responses and other clinical evaluations are in progress and will be reported upon, separately, in the near future.

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# ALLERGENIC (SKIN-TEST) ACTIVITY OF LOW RAGWEED POLLEN AFTER IRRADIATION OF EXTRACT WITH ULTRAVIOLET LIGHT

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THE purpose of this experiment was to learn whether ultraviolet irradiation, at levels approximating those employed for atmospheric sterilization, exerts any effect upon either the potency or the specificity of pollen extract, as judged by direct and indirect cutaneous tests.

Numerous studies of the effect of ultraviolet rays upon antibodies and antigens have appeared in the recent literature. Kondo<sup>5</sup> investigated the influence of such treatment upon lysin for bacteriophage. Stowens<sup>16</sup> studied the effect of irradiation upon the antigenicity of worm extract. Others have investigated the influence of ultraviolet light upon bacteria (Lea and Haines,<sup>6</sup> and Appling and Tanner<sup>1</sup>), viruses (Levinson,<sup>10</sup> and Henle and Henle<sup>7</sup>), and upon fungi (Emmons and Hollaender,<sup>3</sup>) Hart<sup>4,5</sup> turned the bactericidal action of ultraviolet light to practical use when he employed it to sterilize the atmosphere of operating rooms. Salk, Lavin and Francis,<sup>15</sup> Morgan and Lavin,<sup>13</sup> Levinson<sup>10</sup> and others have inquired into the problem of inactivating bacterial and viral vaccines by exposures which did not reduce the immunological potency of the material. Loss of antigenicity, reported by earlier experimenters, was probably due to heating rather than to irradiation. Casals<sup>2</sup> and Havens et al<sup>6</sup> produced a number of neurotropic viral vaccines which retained their complement-fixing qualities after exposure to ultraviolet light. Antigens prepared with these viruses by usual methods, which involve the use of heat or of chemicals for sterilization, commonly are unsatisfactory for complement-fixation. Repetto<sup>14</sup> observed the effect of ultraviolet rays upon diphtheria toxin, toxoid and antitoxin. Woglom and Warren<sup>17</sup> found that the Shope papilloma virus retained its immunizing power after irradiation.

## MATERIALS AND METHODS

*Preparation of Antigenic Solutions.*—The extract of low ragweed pollen used for these experiments was prepared and irradiated by the Arlington Chemical Company. Irradiation was carried out using a Hygeaire sterilizing unit equipped with a 30-watt General Electric germicidal lamp. The entire unit was inverted over a tabletop in such a manner that the distance between the tube envelope and the tabletop was 6 inches, and solutions placed on the table in small vials or flat dishes received both the direct and the reflected rays from the lamp. According to manufacturers' bulletins, 85 per cent of the radiant energy output of these lamps is confined to the

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wave length 2,537 Ångstrom units. The possibility of ozonolysis is minimized, since ozone production is stated at all times to be below one part in ten million parts of air.

One portion of the extract of low ragweed pollen was subjected to irradiation at 6 inches through a glass barrier for one hour, whereas another portion was similarly treated without the glass barrier and for a period of thirty minutes. The former portion, along with its non-irradiated control solution, had been previously sterilized by passage through a Berkefeld filter, whereas the other solutions were rendered bacteria-free by filtration through sintered glass following the irradiation treatment.

The original extract was standardized upon its nitrogen content, 0.1 mg. of phosphotungstic-acid-precipitate nitrogen representing 10,000 "protein nitrogen" units. Each batch of solution was finally diluted in physiological saline solution to give the following testing strengths per milliliter of extract: .001, .01, .1, 1, 5, 10, and 100 units.

*Technique of Direct Testing.*—Cutaneous tests were performed on the patient's right arm. Using a 0.25 ml. syringe, .02 ml. of antigen in graduated strengths were intracutaneously injected into duplicate sites along the lateral and medial aspects of the arm. The concentrations selected were such as to produce responses ranging from negative to definitely positive, with the aim of establishing the threshold dose after the method of Loveless.<sup>11</sup> The practice of placing one test high in the lateral aspect of the arm and its duplicate lower in the medial portion and using the average as the basis for judgment tends to minimize variation in the reaction to a given dose because of location.

The subjects chosen for direct testing were patients who were pollen-sensitive but untreated for at least ten months. All had received their past therapeutic injections in a limited area of the right arm, which was meticulously avoided during the present experiment, so as to eliminate any residual effect of local immunity.

Twenty minutes after the test solutions had been injected, wheals and their surrounding flares were carefully outlined on the arm in ink. The patterns were subsequently transferred onto tracing paper for later study.

*Procedure for Cross-neutralization Studies.*—An equal volume of serum from an untreated, ragweed-sensitive patient was introduced into each of four sterile Wassermann tubes. Into each tube an equal amount of one of the irradiated antigens, or of its control solution, was added. After mixing, 0.1 ml. from each tube was injected intracutaneously into the back of a normal subject in four successive sites. The next day, one of these four sites was tested with the antigen originally present in the mixture in order to make certain that the site was specifically exhausted. Thereafter, each of the other sites was successively tested with one of the other antigenic solutions and any tendency to react noted.

# RAGWEED POLLEN—BROWN AND LOVELESS

TABLE I. ALLERGENIC (SKIN-TEST) ACTIVITY OF POLLEN EXTRACT  
WAS ESSENTIALLY UNCHANGED BY MILD IRRADIATION  
WITH ULTRAVIOLET LIGHT

Allergic Patient Tested	Strength of Pollen Extract Eliciting Threshold Response (P. N. Units/ml)		Difference in Threshold Dose
	Before Irradiation	After Irradiation	
		At 6 inches for 1 hour through glass	
1. Fei	.1	.1	none
2. McK	.02	.1	questionable
3. Kun	.01	.02	not significant
4. Rei	.1	.02	questionable
5. Leo	.02	.01	not significant
6. You	.02	.01	not significant
7. Sha	.1	.01	questionable
8. Str	.1	.01	questionable
9. Qrk	.001	.001	none
		At 6 inches for ½ hour without barrier	
10. Sei	25	10	questionable
11. Poe	7	5	not significant
12. Shan	5	5	none
13. Rei	5	5	none
14. She	1	5	questionable
15. Ita	1	1	none
16. Fri	1	1	none
17. Cra	1	1	none
18. Man	1	1	none
19. Leon	1	1	none
20. Shl	1	1	none
21. McK	1	1	none
22. Dan	.5	.5	none
23. Lur	.1	.1	none
24. McKs	.1	.1	none
25. Qun	.1	.1	none
26. Hen	.5	.1	questionable
27. Chr	.01	.02	not significant
28. DeR	.01	.01	none

## FINDINGS

Table I shows the approximate threshold doses of irradiated and control solutions tested in twenty-eight allergic patients. In sixteen instances, the results were the same with either solution; in seven others the difference was of questionable significance, and in five of no significance. It was concluded, therefore, that irradiation of low ragweed extract with the doses of ultraviolet light employed had no impressive effect on the allergenicity of the solutions as far as their cutaneous reactivity was concerned. Cross-neutralization experiments led to the same conclusion. Mixtures of reaginic serum and any of the pollen solutions gave rise to immediate wheal and flare reactions when intracutaneously tested in normal subjects, but no further response was noted when the original solution or any of the other solutions was again introduced into the sites on the following day. In other words, irradiated and control solutions behaved in a like manner, which indicated that neither the potency nor the specificity had been grossly altered by exposure to ultraviolet rays.

## SUMMARY AND DISCUSSION

The effect of ultraviolet irradiation upon the skin-test activity of ragweed pollen extract has been tested by establishing the approximate threshold doses of two differently irradiated solutions and of their control, non-irradiated samples, in naturally sensitive cases. No significant differences were noted in the activity of the four specimens, which were derived from one original extraction of pollen. That the potency and specificity of the irradiated samples were essentially unaltered was indicated again by the similarity of results with cross-neutralization tests. The degree of exposure to the rays had been similar to that employed by others for purposes of sterilizing the atmosphere.

Both tests employed by the authors deal with the union of allergen and *reagin*, or sensitizing antibody, as revealed by the urticarial response in naturally sensitive or experimentally sensitized skin. Similar tests could have been carried out in the allergic conjunctiva with a view to determining the relative threshold doses of irradiated and non-irradiated solutions.

Before final conclusions can be drawn regarding the use of ultraviolet irradiation as a means of reducing the chance of atmospheric contamination during routine manufacture of sterile allergens, it will be necessary to determine whether the immunizing powers of these solutions are altered by ultraviolet light. This can be tested by observing the production of thermostable antibodies<sup>12</sup> in either nonatopic or allergic individuals, comparisons being drawn between the control and the irradiated antigen.

The authors wish to thank Mr. Robert A. Harte, of the Arlington Chemical Company, for his preparation and irradiation of the pollen extracts as well as for helpful advice; and Dr. Horace S. Baldwin for his co-operation.

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# ALLERGIC PROBLEMS OF THE GASTROINTESTINAL TRACT

## Report of Cases Seen in Military Service

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THE important role played by gastrointestinal disturbances in military service is clearly evident from the statistics in the annual reports of the Surgeon General. The report for 1940 ranks gastrointestinal disease as the third cause for admission to sick report, the fourth as a cause of death, and the fifth as a cause for disability.

Diseases referable to the gastrointestinal tract occurring in military and civilian life are essentially the same. If we accept this as a fact, we must more accurately evaluate 18 to 25 per cent of patients diagnosed as suffering from digestive neuroses or functional gastrointestinal disturbances. This percentage of nonorganic gastrointestinal disease is not confined to the hospitals of the United States. Graham and Kerr<sup>5</sup> report that in one military hospital in England 24 per cent of the gastrointestinal cases were functional in nature. Tidy,<sup>15</sup> also of Great Britain, reviewed 2,500 dyspeptic patients admitted to several military hospitals and found that such cases constituted 35 per cent of the total. This large group of patients were placed in the category as having a constitutional psychopathic state or some type of neuroses.

In an article by John L. Kanter, M.D.,<sup>7</sup> Colonel in the Medical Reserve, no mention is made of the probable role played by allergy in the gastrointestinal tract. Rowe,<sup>10</sup> Andresen,<sup>2</sup> Alvarez<sup>1</sup> and others have pointed out that, during fluoroscopic studies, allergic reactions will take place in the stomach when milk, chocolate, buttermilk or other foods to which a patient may be hypersensitive are included in the test meal.

The chief clinical forms of allergy are easily recognized. This paper is concerned, however, with those conditions which are definitely allergic but, not being readily apparent, are often troublesome to identify. There are two chief groups of such vague conditions. The first group really comprises the atypical forms of the usually evident allergic complaints, the identifying signs of which are so slight, so indefinite or so involved with the symptoms of complicating conditions that it is difficult to recognize the typical allergic syndrome. The second group is composed of allergic varieties of such conditions as gastrointestinal disturbances, eczema and headache. Here the identification of the allergic status is often confusing since the symptoms are usually indefinite and nonspecific, being frequently shared with nonallergic conditions. It is with the gastrointestinal manifestations as seen in this second group that this paper is concerned.

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Presented at the Southeastern Allergy Association Session, January 18, 1947, at the Atlanta Biltmore Hotel, Atlanta, Georgia.



Frequently these vague hypersensitive conditions are linked with more definite hypersensitive conditions; the history of an associated bronchial asthma, hay fever or urticaria may be the clue which permits the establishment of the more obscure complaint upon an allergic basis. Again, the presence in the family history, collateral or antecedent, of clinical allergy is of significance since it has been definitely established that the tendency to many forms of the hypersensitive state is an inherited trait. Positive skin tests, scratch or intradermal, very often afford conclusive evidence, but in those individuals in whom the skin tests are negative, the allergic basis may be established by studying the clinical symptoms resulting from a direct test of the patient with the suspected substance. In food problems the "trial and error" method or restrictive diets may be used. Blood eosinophilia and leukopenic index studies may also assist in the diagnosis.

The gastrointestinal manifestations of allergy are caused chiefly by the ingestion of foods, drugs, pollens and bacteria and are due largely to the direct contact of the ingested substance with the mucous membrane, or as a part of the general reaction after the protein has been absorbed through the mucous membrane. They may be due to absorption following inoculation. The severity of these reactions may well be appreciated when one considers the intimate relation of the allergen to the sensitized wall (shock organ) of the alimentary tract.

The allergic gastrointestinal cases may be divided according to whether the reaction was immediate or delayed and/or according to the anatomic location of the reaction.

The *immediate* reaction is exemplified when the time between the ingestion of a food and the reaction varies from several seconds to several hours, and the delayed reaction when the time interval varies from four hours to several days. In the first group, the symptoms can never be considered as vague. They are so prompt and usually so intense that the cause and effect are immediately apparent. The acute reaction is exemplified by the patient who is so sensitive that faintness, nausea, vomiting and diarrhea regularly develop within a few moments following ingestion of an allergic food. Substances causing immediate alimentary reactions are apt to be associated with positive skin tests. It is, therefore, justifiable to skin test with all foods, especially in patients who present a strong history of allergy. The offending foods will usually react by skin test.

The delayed reaction is less frequently recognized since it is more obscure. Here the interval between ingestion and reaction is longer, often two or three days or more; the symptoms present are not specific for allergic conditions. The patients who complain of "indigestion" may be considered as presenting this type of reaction.

Rowe<sup>12</sup> and others have classified many symptoms such as anorexia, eructations, pyrosis, epigastralgia, postprandial nausea, vomiting, and abdominal distress, as often associated with gastrointestinal disturbance or

functional states but found in many patients in whom no organic disease was discovered and in whom allergic investigations demonstrated the presence of a food hypersensitivity. Since the longer reaction time confuses the picture, the patient rarely knows the food excitant and, indeed, is often unaware that a food is responsible.

#### DIAGNOSIS

The diagnosis of a gastrointestinal allergy necessitates a very careful and detailed history, which may be deceptive because allergic symptoms may resemble those due to actual disease, especially since both conditions may co-exist. When allergy is suspected, it is essential to do thorough gastrointestinal studies. The presence of allergy is to be suspected when the history produces any of the following factors:

1. A family history of allergy, bearing in mind the familial tendency of allergy, and remembering that neither the specific type sensitiveness nor the character of the complaint is inherited, but merely the ability to become allergic.

2. A previous personal history of associated allergic reactions such as recurring skin allergy, recurrent attacks of upper respiratory allergy, so-called sick headaches or migraine and the occurrence of heartburn or diarrhea after certain foods.

3. The occurrence of periodic and vague gastrointestinal symptoms at irregular or regular intervals in institutionalized individuals. (Eating of the same foods on the same day of each week.)

4. The onset of manifestations at a physiological period of life such as puberty, pregnancy, the menopause or after some emotional shock.

5. The diagnosis can be further established by carefully studying the physiological pathology of the manifestations involved. The gastrointestinal manifestations of allergy consist, as in the case of allergy of the upper respiratory tract essentially of two types of reactions: (1) mucous membrane involvement with activity of glands, blood eosinophilia, lymphocytosis and edema; (2) muscular reactions of both spastic and hypotonic character, motivated through the nervous system, mediated perhaps by the formation of a histamine-like substance.

The mucosal manifestations may be mild or quite severe and extensive. There may be local areas of hyperemia about the mouth, esophagus, stomach, intestines, rectum, or generalized reactions throughout the entire gastrointestinal tract, resembling inflammation and producing similar, though at times temporary, reactions.<sup>6,11</sup> Angioneurotic edema may be local or general, invading merely the mucosa or the entire wall. When such reactions affect the intestine or any hollow viscus, symptoms of acute obstruction may appear. Areas of ischemia or edema may occur, resulting in necrosis, ulceration or hemorrhage. At the Cleveland Clinic the above

phenomena have been observed by direct gastroscopic and proctoscopic examinations following the application or injection of the allergen.

Just as in "canker sores," small mucosal ulcers in the mouth may be of short duration. Small gastric or duodenal ulcers may also occur and quickly disappear. There may also be submucosal hemorrhages if the petechial or purpuric areas occasionally seen in the rectum or sigmoid colon break down and bleed. Repeated occurrence of the more severe reactions will finally result in fibrosis, and if chronic irritation constitutes a factor in the production of carcinoma, allergy must be considered as a possible cause of this condition.

The variable muscular manifestations consist of motility disturbances; hypermotility, hypomotility, atony or reverse peristalsis.<sup>3,4</sup> Increased motility may be interpreted as "gas," colic or diarrhea. Diarrhea associated with mucous membrane ulcerations and hemorrhages may give the picture of ulcerative colitis. Hypomotility often associated with a spastic colon may be manifested merely by constipation or, when severe and associated with mucosal changes, may suggest actual obstruction. Spastic contraction may occur in any part of the gastrointestinal tract, and although many are considered as functional states, it is undoubtedly true that an otherwise unexplainable spasmodic condition may be entirely due to allergy. These include esophageal spasm, cardiospasm, pylorospasm, colonic spasm and also anal sphincter spasm. As a rule, the manifestations involving the mucous membrane also extend to the muscular system.

X-ray studies may also be of value in the diagnosis in that they may demonstrate mucous membrane and muscular evidence of allergy. This is especially true if spasticity and hypermotility of the small or large intestine, or the peculiar appearance due to angioneurotic edema of the stomach or intestines, are present as an allergic reaction. Evidences of chronic lesions, such as ulcerative colitis due to prolonged ingestion of offending foods, give the most marked roentgenological pictures and appear similar to those lesions seen as due to other causes.

In gastroscopic examination after the ingestion of the specific antigenic food substances, the characteristic reactions observed are distinct hyperemia, sudden edema of the mucosal folds, presence of grayish mucus and minute hemorrhagic areas and hyperperistalsis.<sup>9</sup> These reactions are suggestive of allergy. Proctoscopically, one may note the development of erythema, edema and occasionally hemorrhage.<sup>14</sup> Pathologically, typical tissue studies may reveal evidence of edema, inflammation, exudation, numerous wandering cells and round cell infiltration with a predominance of eosinophilic cells. Fecal necrosis with ulceration and hemorrhage may also be noted.<sup>8</sup>

Discovering the allergic cause is the major part of the diagnosis. It should be stressed that the presence or absence of skin test reactions is not the one deciding factor in establishing a diagnosis of allergy. It is frequently true that the presence or absence of skin reactions is of para-

mount value only when interpreted in relation to a specific type of allergy and the present clinical problems. It is essential in each instance to prove the clinical relationship of the supposedly causative substances. It is necessary for the patient to keep a careful record of all foods or drugs ingested together with notes on symptoms in relation to the contact with these foods and drugs. It must be understood that whenever a small quantity of food or other item to which a patient is hypersensitive is ingested, a reaction will result, and that one food alone is rarely responsible in a given case.

#### TREATMENT

The treatment of gastrointestinal allergy consists of:

1. The relief of the acute attack.
2. The prevention of future attacks.

In relief of acute attacks where an acute surgical abdominal emergency is suspected and operation considered, it may be desirable to apply some harmless therapeutic measure which would increase gastrointestinal motility and, at the same time, not endanger the patient's life. The drug of choice is, of course, epinephrine (1:1,000) in doses of 0.3 to 0.5 c.c. subcutaneously. This has been known to produce spectacular results. Ephedrine (3/8 grain) has been used orally to good advantage following the immediate acute attack. Pituitrin, calcium and parathyroid have been used with moderate success in some instances when epinephrine has failed or proven undesirable.

In those cases where the acute reaction is known to be allergic and due to food factors, lavage, catharsis, enemata or intravenous fluids (especially glucose saline) may be of value. Castor oil and magnesium sulphate are the excellent cathartics for this purpose.

In the prevention of future attacks following recovery from the acute attack, a complete allergic survey is essential. The subsequent care of the patient in respect to desensitization and dietary restrictions must then be governed by this allergic examination.

Physicians interested in allergy<sup>13</sup> have suggested diets of different types, with varying degrees of success. Experience has proven that success in the solution of an alimentary allergy depends on a co-operative patient, and then only when the patient has been intelligently advised of the principles underlying the restrictions and additions regarding the various allergens. Here, too, the physician must remember that too restricted diets over long periods may do greater harm than good, and his ingenuity will be taxed to the utmost to advise both a palatable and a physiologically complete diet.

The following five cases were merely typical of the larger number seen in the allergy clinic and in consultation with the Gastrointestinal Section. The first two cases, were of more than usual interest because of their similarity to conditions other than allergy and are, therefore, presented in

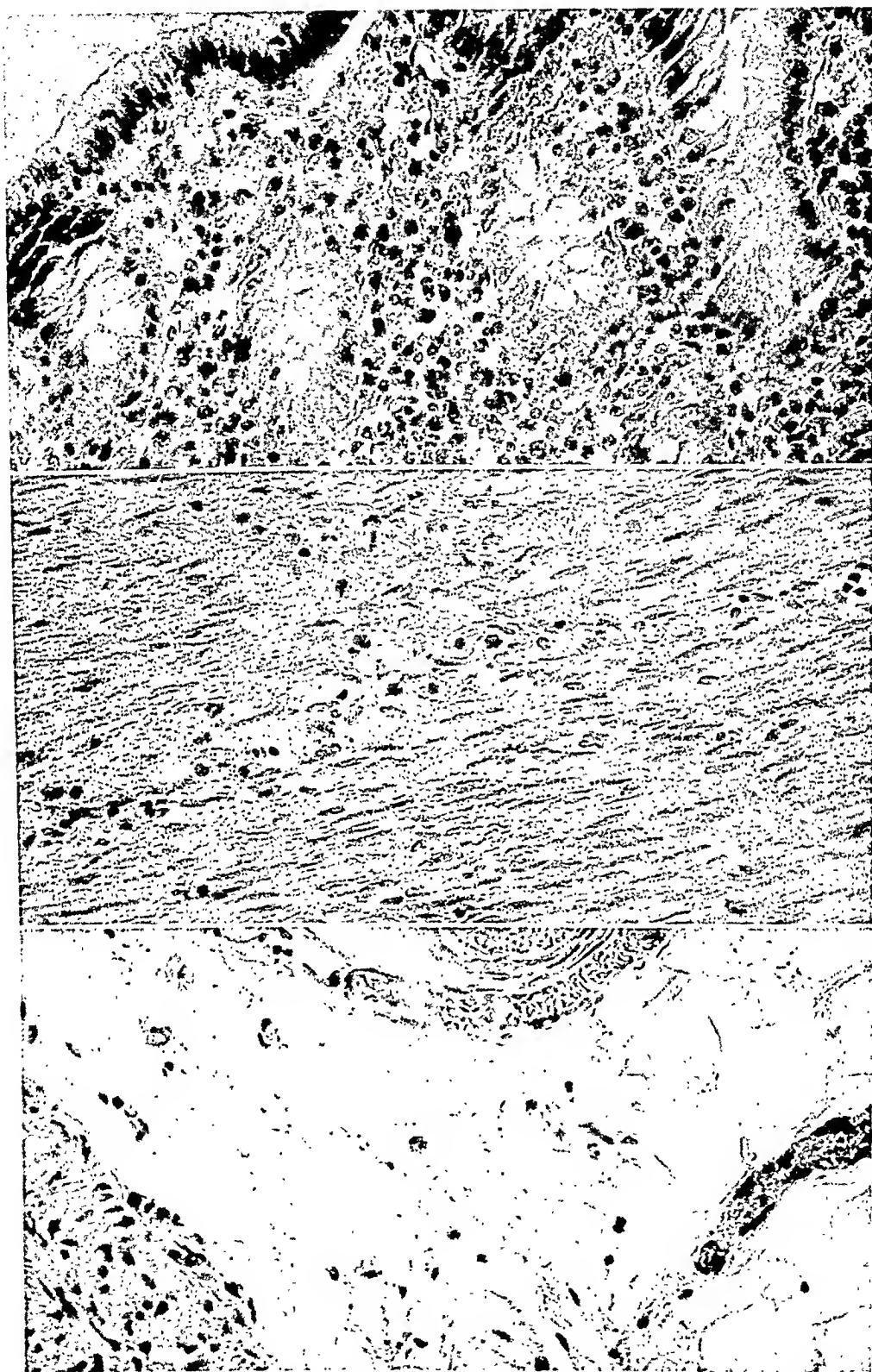


Fig. 1. (Above) Photomicrograph shows mucosa with some edema, numerous wandering cells, eosinophil cell colonies.  
 (Center) Photomicrograph shows muscle with edema and round cell infiltration, eosinophil cells predominating.  
 (Below) Photomicrograph shows serosa, with congestion and edema, some round cell infiltration containing eosinophiles.

more detail and with photomicrographs. From January, 1943, to January, 1946, the Allergy Section saw 197 patients having symptoms referable to the gastrointestinal tract, of whom 163 had complete gastrointestinal studies, with negative findings. Of these, 118 (60 per cent) had from fair to excellent relief following allergy studies and treatment.

#### REPORT OF CASES

*Case 1.*—A woman, aged twenty-one, presented a history of recurring attacks of bronchial asthma mild in degrees for a period of ten years. Her father suffered from bronchial asthma. Six months previously she had had an acute attack of right lower quadrant pain and other clinical signs of acute appendicitis, except for a normal polymorphonuclear count and an 18 per cent eosinophilia. No operation was performed. Subsequent differential counts revealed a gradual return of the eosinophilia to normal limits. Three months following the first attack, a second attack similar to the first was experienced, and while undergoing allergy studies, a third attack occurred. At this time the differential blood count revealed a polymorphonuclear count of 7,800 and an eosinophilia of 23 per cent. The clinical impression was acute allergic appendicitis. Because of the frequency of attacks and the dangers of obstructive symptoms which could develop due to prolonged edema in the presence of an associated fecalith, an appendectomy was performed.

Pathologically, a histological diagnosis of allergic appendicitis was made on the basis of edema and congestion of serosa, muscle and mucosa, associated with numerous wandering cells, round cell infiltration and the predominance of eosinophil cells (Fig. 1).

The authors wish to acknowledge their appreciation to Dr. B. S. Kline, Mt. Sinai Hospital, Cleveland, Ohio, for his kindness in reviewing the histological slides and making the photomicrographs available; to Major Gregory N. Brown, pathologist, Oliver General Hospital, Augusta, Georgia, who originally confirmed the clinical impression pathologically; to Major J. Budetti for his diagnostic esophagoscopy.

*Case 2.*—A man, aged twenty-seven, was originally hospitalized because of nausea, hematemesis and melena. A diagnosis of cirrhosis of the liver was made following radiological studies which demonstrated multiple space-filling lesions of the distal esophagus which were interpreted as esophageal varices. He was transferred to a general hospital, and subsequent x-ray studies revealed the same radiological deformity of the distal area of the esophagus (Fig. 2). However, the patient's history and laboratory studies did not support the previous diagnosis of cirrhosis of the liver.

Since there was a history of mild bronchial asthma since childhood, associated with a 6 per cent eosinophilia and a history of urticaria in his son, esophagoscopy was done and this examination revealed a prominence of the rugae in the distal one third of the esophagus, associated with a pale boggy mucous membrane. No polyps or varicosities were found, although in areas the rugae were almost polypoid in size and swelling. A mucosal biopsy was taken and subsequent histological studies revealed edema and a hypersecretory state of the glands, plus a moderate eosinophilia which was compatible with the reversible sequence in early allergy (Fig. 3).

Subsequent observations and clinical studies revealed progressive improvement of the radiological, pathological and esophageal appearance. The patient was asymptomatic from a gastrointestinal standpoint upon his discharge from the hospital.

*Case 3.*—A man, aged thirty-six, for many years had experienced episodes of diarrhea, averaging two to six foul smelling stools daily for three to five days. From

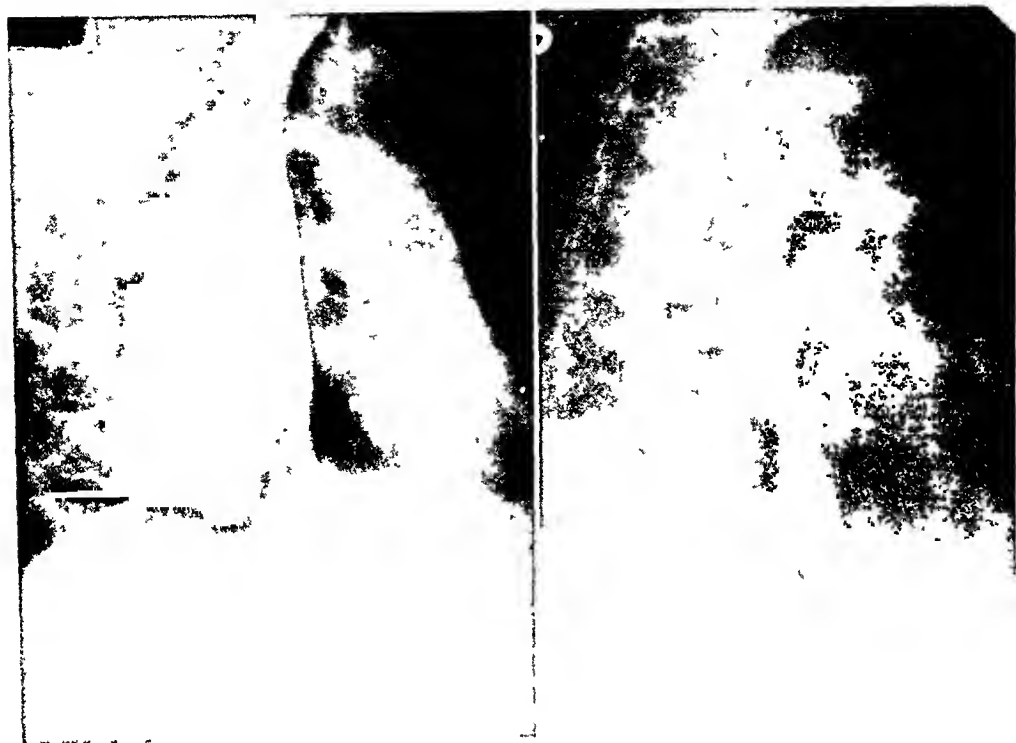


Fig. 2 (Left) Shows ragged moth eaten appearance of distal esophagus suggestive of varices. (Right) Reveals marked improvement

the age of twelve to twenty he had repeated attacks of urticaria which ceased when he stopped eating tomatoes. In 1938, he began to experience summer episodes of mild attacks of wheezing and coughing. In 1940, he had a conjunctivitis for two weeks and later developed recurrent attacks of low back pain. In 1943, a tonsillectomy was done without benefit. He was hospitalized, and studies of foci of infection were done but no evidence of infection was found. Orthopedic studies were negative. Gastrointestinal examinations were normal except for a slight spasticity of the descending colon and a thrombosed internal hemorrhoid. A nose and throat examination revealed a bilateral allergic conjunctivitis and chronic allergic rhinitis. Laboratory studies were essentially negative.

Subsequent allergy studies revealed the following skin test reactions: marked reactions to pork, corn meal, white potatoes, tomatoes, coffee, cantaloupe, lemon, peach, pear and beef; moderate reactions to wheat, oats, carrot, lettuce, onion, dust and ragweed.

A diagnosis of constitutional allergy involving the respiratory and gastrointestinal system was made. The patient was placed on a diet and a multiple hyposensitization regime, with excellent results. He returned to duty. Numerous follow-up personal communications (J.R.) with him have revealed that he has continued his diet and injection therapy and that he has remained completely well.

*Case 4*—A man, aged twenty-four, first experienced eczema on his neck and face at the age of ten when he lived on a dairy farm. This recurred and later became generalized, especially during cold weather. At sixteen years of age he experienced furunculosis during the winter. During his adolescence he began to develop recurrent gastrointestinal complaints, especially epigastric pain and constipation which was somewhat relieved by food or catharsis. Following his induction into the army, he

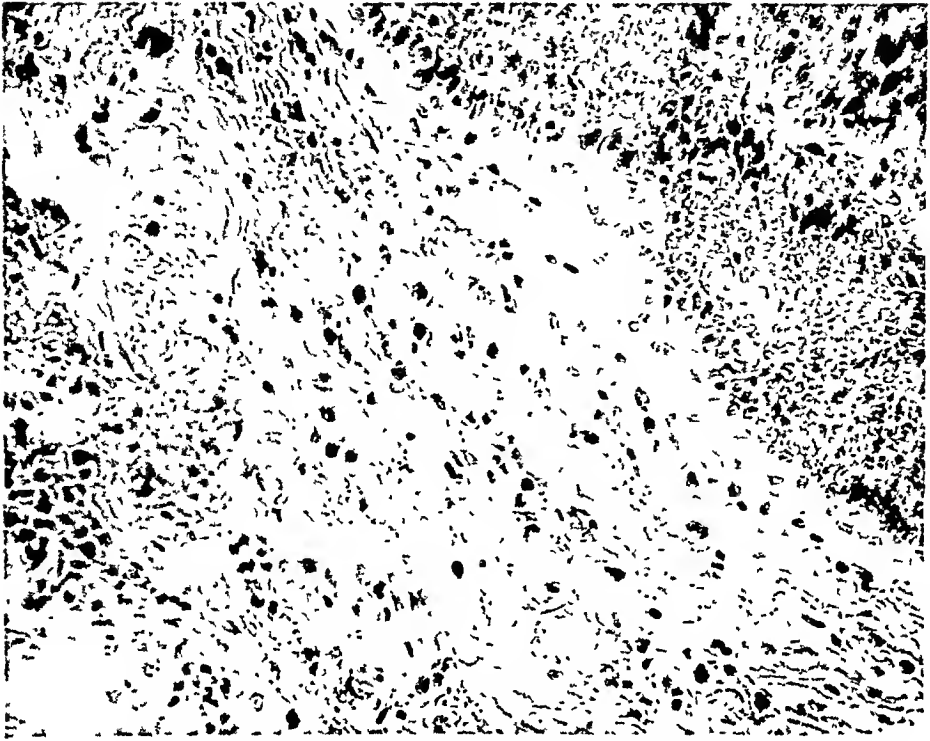


Fig. 3. Esophagus. Photomicrograph shows edema and round cell infiltration below lining epithelium. Leucocytes predominate in the exudate. The picture suggests allergic inflammation.

gained approximately 20 pounds. Eighteen months later, however, he began to lose weight and experienced headaches, dizzy spells, heartburn and water brash. A selective dyspepsia was also noted for onions, fried foods, cheese, bananas, fruit juice and tomato juice. Since his symptoms became progressively worse, he was hospitalized and observed as a possible case of gastritis. Gastrointestinal studies were negative, and an allergic survey revealed that he was markedly sensitive to milk, corn, cauliflower, potatoes, tomatoes, pineapple and walnuts. Following the institution of an allergen-free diet, he remained symptom free.

*Case 5*—A man, aged thirty-two, had experienced episodes of headaches, postprandial fullness, epigastralgia, anorexia, nausea, pyrosis and occasionally vomiting since 1929. In 1935 he was hospitalized for one week and was told that he had a digestive dysfunction. His symptoms continued periodically, and no apparent relief resulted from any type of therapy. His symptoms became so severe that he was rehospitalized in 1943. Complete examinations were done and found to be negative. Allergic studies revealed that he was markedly sensitive to beef, veal, tuna fish, cabbage, tomato, pineapple and haddock. With the elimination of the above foods, this patient obtained almost instant relief, and by following this selective dietary regimen, he was able to return to duty.

#### COMMENTS

At the present time there has been no satisfactory explanation of the physiopathological concept of selectivity in gastrointestinal allergy. Allergic conditions of the oral and anorectal area are more frequently noted, but



then they are more readily accessible in routine examinations. Allergic appendicitis has been demonstrated on several occasions, but as a clinical diagnosis it is rarely made. The writers believe that the presence of gastrointestinal allergy will be demonstrated more frequently in the future, especially when the impression of a good clinical history is verified by detailed endoscopic or tissue studies. Esophageal allergy is not common but should always be considered as a possibility in patients who present abnormalities in this area which are not readily explainable and, particularly so, when such individuals have a history of other allergic manifestations.

The treatment of these conditions is not always satisfactory due to the difficulty of demonstrating the basic allergen, but a great many patients are helped considerably by desensitization and dietary regimen.

#### SUMMARY

Gastrointestinal allergy is a definite entity and cannot be disregarded as an etiology of dyspepsia or other allied complaints. It is much more common than suspected, and undoubtedly many of the so-called functional states or nervous dyspeptics may in reality be due to allergic factors.

A detailed history and thorough clinical studies, including an allergic survey, may be necessary in order to make a final diagnosis in many vague so-called functional disturbances. Treatment when possible should be directed to a hyposensitization and dietary regimen.

Cases of allergic appendicitis, esophagitis and multiple food allergies have been presented as clinical entities, although their symptomatology suggested other organic disease or functional states.

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# BALSAM AS A CAUSE OF CONTACT DERMATITIS IN A FLORIST

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THE following case report adds balsam to the list of plants known to cause contact dermatitis.

## CASE REPORT

Mr. P. H. E., aged 56, a florist was first seen on December 3, 1943, because of a pruritic dermatitis on his face, neck, ears and hands which had been present for two weeks. The eruption began on the neck and wrists and spread rapidly to all exposed skin areas with the exception of the palmar surfaces of the hands. It consisted of pinpoint vesicles, with slight scaling around the hairline and in the creases of the neck and wrists. In the creases there was also beginning lichenification. There was diffuse erythema throughout, and the itching was intense.

A similiar rash had appeared first in 1940, about November 20, lasting until January 10 of the following year, 1941; it had reappeared each year thereafter during the same period.

Although the itching was intense at night, especially in bed, the patient was convinced that the rash was caused by something in his flower shop. There were no new contacts in his home during the period of his symptoms.

For the past three seasons, the patient had been under the care of a dermatologist, who agreed that the condition was a contact dermatitis, probably from some plant. He had tried topical treatments of all sorts, intravenous calcium and x-ray, all to no avail.

The dermatitis recurred each year at the time the Christmas greens and decorations were brought into the patient's flower shop. These included painted grasses, pine and pine cones, cedar and balsams. The flowers the patient handled during this period were roses and chrysanthemums, both of which were in his shop long before the appearance of the eruption. Knowing of the frequent occurrence of dermatitis from primroses, he never had had them in his shop. The patient thought his skin was worse when handling balsam, especially when he was breaking branches for sprays and wreaths. In 1943, the year he appeared for treatment, he refused to touch any balsams; nevertheless the rash appeared as before.

The present history of the patient was negative for other forms of allergy, but as a child, he had had a severe eczema of the face, neck and scalp.

The family history was negative for allergy as far as he could recall.

Arrangements were made for patch tests. Branches of balsam, pine and cedar were sent from the shop. An oil extract of each was prepared according to the technique of Shelmire and Black.<sup>2</sup>

Before the patient returned for application of the patch tests, he became ill with the then current grippe infection and was home in bed for three days. During that time the rash disappeared completely, but recurred twenty-four hours after his return to the shop.

On December 17 patch tests were applied for balsam, cedar, dog hair, wool, chrysanthemum. When the tests were removed twenty-four hours later, all were negative except the one for balsam. At this site there was a vesicular reaction about half the size of a dime, recorded as 2-plus. Two days later, the site of this test, which was on his back just below the collar line, had enlarged to the size of

\*Read before the Chicago Society of Allergy, April, 1945.

## BALSAM AS A CAUSE OF CONTACT DERMATITIS—KAPPES

a silver dollar and coalesced with the rash on the neck, which had become intensified in this area.

The treatment decided upon was oral desensitization. The oil extract of balsam was diluted 1:100 in Mazola according to Shelmire's directions,<sup>1</sup> and the patient was directed to take one drop in milk or fruit juice daily for three days, then increase one drop a day to maximum of five drops. He was also given Lowilla Cream (Westwood Pharmacal Company, Buffalo) to use as a protective coating when in his shop.

He was asked to report immediately after Christmas, but nothing was heard from him until January 15. The extract had been used as directed until the maximum dose of five drops had been taken for three days. Then he had stopped the treatment because the dermatitis seemed worse, but had resumed it after a week. He had taken a series of doses daily for several days, three different times, and each time he thought the eruption had been accentuated. This was considered a good indication that the extract was potent and specific, but that the dosage was incorrect.

The only local applications used were Lowilla Cream with a bland cold cream base. This proved very helpful as a protective coating, but was in no way curative.

He was advised to return the following fall to receive directions for preseasonal treatment, but in November, 1944, he was hospitalized for a cholecystectomy. He returned to his florist shop ten days before Christmas. Having some of the balsam extract in oil left from the preceding season, he started oral therapy at once according to the original directions. He took one drop a day for three days, increased a drop a day to a maximum of five drops, and then stopped. No rash appeared.

It is true that the period of exposure was shorter than usual and the intensity of the exposure somewhat less, because being convalescent, the patient spent most of his time in the office of his shop which was enclosed on three sides. However, he was in and out of the shop itself as well as the workroom where the wreaths and sprays were made. At no time during that season did he have any dermatitis, whereas in other years it had been present constantly from late November until the middle of January.

Before the next Christmas season, 1945-46, the patient had partially retired from his business and made it a point to keep out of the shop when balsam was on hand. Further testing of the oral desensitization was, therefore, not possible.

### SUMMARY

A case of contact dermatitis due to balsam is reported. Oral desensitization with an oil extract of balsam was attempted.

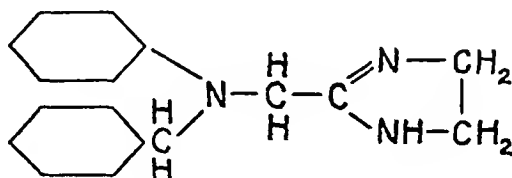
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# AN EVALUATION OF ANTISTINE, A NEW ANTIHISTAMINIC SUBSTANCE

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ANTISTINE is a new synthetic antihistamine substance with the following structural formula:



2 (N-phenyl-N-benzylaminomethyl) imidazole

Animal experiments reveal that the drug has a relatively low toxicity, and exhibits both antihistamine and antianaphylactic action in the intact animal and isolated muscle preparation.<sup>7</sup> Reports in the European literature concerning the use of this new substance in certain allergic conditions have been favorable enough to warrant further investigation of both its antihistaminic and antiallergic actions.<sup>2,9</sup>

TABLE I. PROTECTIVE EFFECT OF ANTISTINE AGAINST HISTAMINE IN THE GUINEA PIG

Antistine mg./kg.	Histamine mg./kg.	Number of Animals Injected	Mortality Per Cent
Control	0.4	10	100
3	0.4	10	30
6	0.4	10	20
10	0.4	10	0
3	0.8	10	100
6	0.8	10	100
10	0.8	10	40
15	0.8	10	0

## ANTIHISTAMINE ACTION IN THE GUINEA PIG

Male guinea pigs, 300 to 450 grams in weight, were injected intraperitoneally with 3 to 15 mg. per kg. of Antistine\* 15 minutes prior to the intravenous injection of varying doses of histamine† (Table II). The 100 per cent lethal dose by this technique is 0.4 mg. per kg. of histamine base.<sup>5</sup> Significant protection against this fatal dose was observed when 3 to 6 mg. per kg. of antistine was administered to each animal prior to

\*From the Departments of Bacteriology and Medicine, Wayne University College of Medicine, Detroit, Michigan.

†The experimental work reported in this study was supported by a grant from Ciba Pharmaceutical Products, Inc., Summit, N. J.

\*Antistine was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

†Histamine Phosphate was furnished by Burroughs Wellcome and Co., (U.S.A.) Inc.

the injection of histamine, while 10 mg. per kg. of the drug protected all guinea pigs against this amount. When two lethal doses (0.8 mg. per kg.) of histamine were administered, 15 mg. per kg. of Antistine was re-

TABLE II. COMPARATIVE ANTIHISTAMINE ACTIVITY IN THE GUINEA PIG

3 mg./kg. of Protective Drug	Number of Lethal Doses of Histamine Necessary to Produce 100% Mortality
Antistine .....	2
Benadryl .....	5
Antergan .....	6
Pyribenzamine .....	37
Neo-antergan .....	124

TABLE III. CLINICAL RESULTS WITH ANTISTINE

Condition Treated	Number of Cases	Helped		Not Helped	
		Number	Per Cent	Number	Per Cent
Bronchial Asthma	24	9	37.50	15	62.50
Vasomotor Rhinitis	59	35	59.32	24	40.68
Urticaria:					
Acute	10	7	70.0	3	30.0
Chronic	9	3	33.34	6	66.66
Penicillin	1	0	0.0	1	100.0
Allergic Headache	6	1	16.67	5	83.33
Atopic Dermatitis	5	3	60.0	2	40.0
Contact Dermatitis	6	3	50.0	3	50.0
Unclassified Dermatitis	2	0	0.0	2	100.0
Pruritis Ani	1	0	0.0	1	100.0

quired to protect all guinea pigs against fatal shock. A comparison with other antihistamine drugs tested in this manner reveals a smaller degree of protection against histamine on the part of Antistine as compared to Benadryl, Pyribenzamine, Antergan, and Neoantergan<sup>6</sup> (Table II).

#### CLINICAL EVALUATION

Antistine was employed in 100 patients with one or more allergic complaints (Table III). Where effective, the drug produced symptomatic relief for periods of two to twelve hours, similar in nature to that exerted by other antihistamine drugs.<sup>3</sup> The degree of palliative action experienced, varied from patient to patient and frequently differed in the same patient from time to time. Successful action was recorded when appreciable amelioration of symptoms was noted following the use of the drug, and difficulty recurred upon withdrawal.

Fifty to 100 mg. four times daily, following meals and at bedtime, were prescribed in the average case, although considerable variation occurred depending on the needs of the individual patient. Doses of 50 mg. were first prescribed, and increased to 100 mg. after twenty-four hours if a beneficial action did not occur and no side effects were produced by the lower dosage. Where symptoms were more intensive, the

drug was administered every two to four hours. In children, doses of 50 mg. four times daily were tolerated without difficulty.

Antistine produced some degree of symptomatic relief in 59 per cent of patients with allergic rhinitis. The effect on rhinorrhea and sneezing appeared to be greater than on nasal blocking. Symptomatic improvement was observed in 37 per cent of asthmatic patients. In these cases, the drug usually benefited the cough to a greater degree than the dyspnea. Seven patients with asthma and associated rhinitis obtained appreciable relief of nasal symptoms, despite failure to affect the asthma. Greater action was apparent in acute than in chronic urticaria, 70 per cent of the former group being benefited, while only 33 per cent of the patients with the chronic type were improved. In one case of severe penicillin "serum sickness" type reaction, Antistine failed to relieve the symptoms. The pruritis accompanying 60 per cent of the cases of atopic eczema and 50 per cent of those with contact dermatitis was benefited by the drug, while the itching associated with two cases of unclassified dermatitis and one case of pruritis ani of allergic origin was not appreciably helped. Only one of six patients with periodic allergic headache was helped by 100 mg. doses of Antistine.

#### CLINICAL COMPARISON WITH PYRIBENZAMINE

It was possible in many instances to make a clinical comparison between the effectiveness of Antistine and Pyribenzamine in the same individual (Table IV). While it is usually necessary in an evaluation of this type to rely on the patient's own impression as to the relative value of various medicaments, a more objective estimation is sometimes possible. In the present comparison, both drugs were at times prepared in capsule form and alternated without the knowledge of the patient. Placebo capsules were also used in eliminating as far as possible the psychologic factors involved in drug administration.

In fifty-one cases of rhinitis there were fourteen patients whose symptoms were helped only by Pyribenzamine. Eight others found that Antistine was the drug which afforded them symptomatic relief. Twenty-four patients (47 per cent of the total number) obtained some help from either drug. Upon further analysis of the latter group, it was found that ten patients obtained a relatively greater degree of action from Pyribenzamine, as compared to only four patients who found Antistine the more effective drug. Of the total number of fifty-one cases complaining of nasal symptoms, only five patients (9.8 per cent) failed to obtain some benefit from either drug.

The effectiveness of both drugs in asthma was relatively low, though there were again some patients who were helped by one compound and not by the other. Pyribenzamine was usually more beneficial in urticaria. In only one case of this type was Antistine found more helpful. Pyribenza-

TABLE IV. COMPARISON OF ANTISTINE AND PYRIBENZAMINE IN THE SAME PATIENT

Condition Treated	Number of Cases Receiving Both Drugs	Helped by Antistine But Not by PBZ		Helped by PBZ But Not by Antistine		Helped By Either Drug				No Difference		Total Receiving No Help From Either Drug			
		Helped by Antistine But Not by PBZ		Helped by PBZ But Not by Antistine		Total	PBZ Better		Antistine Better		No Difference		Total Receiving No Help From Either Drug		
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Bronchial Asthma	17	3	17.65	3	17.65	2	11.76	1	5.88	0	0.0	1	5.88	9	52.94
Vasomotor Rhinitis	51	8	15.69	14	27.45	24	47.06	10	19.61	4	7.84	10	19.61	3	9.80
Eczema:															
Acute	5	1	7.69	1	7.69	3	23.07	2	15.38	0	0.0	1	7.69	0	0.0
Chronic	7	0	0.0	4	30.77	2	15.38	1	7.69	0	0.0	1	7.69	1	7.69
Penicillin	1	0	0.0	1	7.69	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Allergic Headache	5	0	0.0	1	20.00	0	0.0	0	0.0	0	0.0	0	0.0	4	80.0
Atopic Dermatitis	1	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Contact Dermatitis	4	1	25.0	2	50.0	0	0.0	0	0.0	0	0.0	0	0.0	1	25.0
Unclassified Dermatitis	2	0	0.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0
Pruritus Ani	1	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

mine appeared to be slightly more effective in relieving the distress accompanying pruritic skin conditions. The majority of patients with headache of allergic origin failed to obtain relief from either compound.

TABLE V. SIDE EFFECTS WITH ANTISTINE

Gastrointestinal Upset.....	8
Drowsiness .....	7
Vertigo .....	3
Dryness of Mucous Membranes .....	2
Fatigue .....	1
Palpitation .....	1
Dermatitis .....	1
Diplopia .....	1
Nervousness .....	1
Syncopy .....	1

TABLE VI. COMPARATIVE SIDE EFFECT IN 72 PATIENTS RECEIVING ANTISTINE AND PYRIBENZAMINE

	Number of Patients	Per Cent
Side effects from Antistine	13	18.05
Side effects from Pyribenzamine	28	38.8
Patients with side effects from Antistine able to tolerate PBZ without symptoms	3	
Patients with side effects from PBZ able to tolerate Antistine without symptoms.	18	

## TOXICITY COMPARISON OF ANTISTINE AND PYRIBENZAMINE

Twenty-three per cent of those receiving Antistine experienced one or more side effects from doses of 100 mg. Gastrointestinal symptoms and drowsiness were most commonly encountered, but rarely necessitated discontinuing the drug (Table V).

In a group of seventy-two patients who received both drugs, the incidence of side effects from Antistine was 18.05 per cent, as compared to 38.8 per cent from Pyribenzamine (Table VI). Of the twenty-eight patients who experienced unpleasant reactions from Pyribenzamine, eighteen were able to take an effective dose of Antistine (50 to 100 mg.) without difficulty. The remaining ten individuals experienced essentially the same reaction from either drug. On the other hand, only three out of thirteen patients noting side effects from Antistine were able to tolerate a 50 mg. dose of Pyribenzamine.

## LOCAL USE OF ANTISTINE IN ALLERGIC EYE CONDITIONS

Experimental studies with antihistaminic agents in the past has suggested that failure to produce symptomatic effect in certain cases of allergy may be due to insufficient drug reaching the site of action.<sup>4</sup> The topical use of these substances on mucous membranes has been limited to a great



extent by the irritating properties of otherwise effective concentrations. On the basis of a report by Bourquin,<sup>1</sup> a 0.5 per cent solution of Antistine was employed locally in eleven cases of allergic conjunctivitis. Five patients reported a temporary smarting of the eyes following instillation of the solution. This disappeared within a few minutes, and in only one case was considered severe enough to stop the use of the drug. All but three patients experienced beneficial symptomatic action following the instillation of 1 or 2 drops into each eye, which lasted several hours. One patient reported aggravation of the eye condition by its use, while a second in whom the 0.5 per cent solution was too irritating, experienced a beneficial effect from a 0.25 per cent concentration of the drug. The drops were prescribed as necessary, and in some cases were used as often as every two hours for palliative effect. It appears that this solution offers some promise in the symptomatic treatment of certain cases of allergic conjunctivitis.

#### DISCUSSION

The antihistaminic activity of Antistine as determined in the intact guinea pig is less than 10 per cent of that exhibited by Pyribenzamine. Yet a comparison of clinical activity in allergic patients does not reveal this wide variation. In the average individual a 50 mg. dose of Pyribenzamine appears to have the clinical effectiveness of a 100 mg. dose of Antistine. On the other hand, there are some patients who obtain greater benefit from Antistine even in equivalent doses. This apparent discrepancy in antihistamine effect and clinical action is similar to the lack of correlation determined for several drugs in histamine and anaphylactic shock.<sup>8</sup> It has been observed that while wide variations in the ability of these drugs to counteract histamine shock in the guinea pig exists, a similar difference in protective ability against anaphylaxis is not present. This suggests that histamine may play only a partial role in both the anaphylactic and allergic reactions, and that drugs with increasingly higher antihistamine action, as determined experimentally, will have no greater clinical effect than other of lesser potency. If this is true, the more promising developments in antihistamine therapy will come with the discovery of drugs which are better tolerated by the average patient. In the case of Antistine, an important factor which entitles it to a place in the growing list of useful antihistamine agents is its relatively low toxicity at effective dosage. It is also seen from the comparative study of Antistine and Pyribenzamine in the group of rhinitis patients that a trial of both drugs increased the total percentage obtaining symptomatic relief to 91.2 per cent. This would indicate that where symptoms fail to be affected by one antihistaminic agent, a favorable action may be obtained from the use of another of this series of compounds. It should again be emphasized, however, that Antistine as well as other antihistamine substances are palliative drugs, and no

lasting benefit should be expected from their use. Immunologic investigation and management is still a vital part of proper therapy in allergic disease.

#### SUMMARY

1. Antistine is a new synthetic antihistamine substance with the formula: 2-(N-phenyl-N-benzyl-aminomethyl) imidazolin. Ten mg. per kg. of Antistine was found to protect guinea pigs against one lethal dose of intravenous histamine, while 15 mg. per kg. prevented fatal shock when two lethal doses were administered.

2. Antistine in 50 to 100 mg. doses afforded symptomatic relief in the majority of cases of allergic rhinitis and urticaria. Less benefit was apparent in asthma, atopic dermatitis, contact eczema and allergic headache. A comparison between the action of Antistine and Pyribenzamine in the same patient indicated a greater effect on the part of Pyribenzamine in most instances. A smaller percentage found Antistine superior.

3. A 0.5 per cent solution of Antistine used in the eye produced symptomatic relief of burning and itching in cases of allergic conjunctivitis.

4. Side effects from Antistine were generally less frequent than with Pyribenzamine. In a group of patients in whom the two drugs were compared, it was found in many instances that those unable to tolerate Pyribenzamine could take Antistine in effective dosage without side effect.

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# OBSERVATIONS ON VARIATIONS IN REACTIVITY IN A CASE OF ALLERGY TO PENICILLIN

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ALLERGIC reactions to penicillin have now become well known. Such manifestations of hypersensitivity as dermatitis,<sup>1</sup> asthma,<sup>6</sup> anaphylactic shock,<sup>8</sup> the Arthus phenomenon<sup>7</sup> and the like have all been described following its administration. Kalodny and Denhoff,<sup>4</sup> however, found even in a group of consistent reactors to penicillin "that a phase of relative anergy existed for a period of five to seven days" and noted that skin tests were not consistently positive. Zeller<sup>9</sup> has reported a case which well illustrates the variations in the degree of sensitivity. He points out that as little as 50 units of commercial penicillin sodium will produce urticaria during the reactive phase, but during the anergic state, in his case, the week following the cessation of symptoms, increasing doses of penicillin up to 25,000 units produced no reaction of hypersensitivity. The present case is described because of the variations in reactivity observed and the advantage taken from these observations for therapeutic action.

## CASE REPORT

I. H., a fifty-nine-year-old white woman, was admitted to the Medical Service of the Cincinnati General Hospital, May 1, 1946, because of hypertensive arteriosclerotic heart disease complicated by a large carbuncle of the hip. Penicillin therapy, in dosages of 50,000 units intramuscularly every three hours, was instituted on the day of admission. On the second day of penicillin therapy her temperature rose to 103° F. There was intense redness and edema around each site of injection. A generalized, maculo-papular erythematous eruption was noted, which was most intense over the flexures of the elbows, axillae, and groin. Penicillin injections were stopped. The rash receded and the temperature returned to normal within the succeeding twenty-four hours. The carbuncle was then incised and drained. Two days later 50,000 units of penicillin were given orally every two hours for one day, which did not reproduce the rash. The patient, however, complained of soreness and tenderness of the tongue and mouth. Examination showed the tongue and buccal mucosa to be red and slightly edematous. Penicillin was stopped. The patient improved and was discharged from the hospital May 5, 1946. No skin tests had been done.

The patient was readmitted to the hospital on August 25, 1946, with an acute keratoconjunctivitis. The right eye showed marked edema of the lids and some erythema. The bulbar and palpebral conjunctivae were red and showed ciliary injection. Chemosis was marked. There was a hazy opaque grayish-white infiltration and ulceration about the entire limbus extending across the pupillary area. The aqueous humor appeared to be clear, and the iris was normal in color. The pupil was 3 mm. in diameter, round, nonreactive to light. The red reflex was obtained from the fundus, but due to the corneal haziness no fundoscopic details could be distinguished. The tension was normal to palpation, but the patient was unable to distinguish form. There was some photophobia.

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These studies were made possible under a grant from the Bristol Laboratories, Inc., and in part by a grant from William S. Merrell & Co.

A pneumococcus, type VII, was isolated in pure culture from the right eye. This organism was assayed as sensitive to less than 0.03 units of penicillin per c.c. It was therefore thought desirable that penicillin therapy be given. Because of her history of hypersensitivity reactions on her previous admission, the institution of therapy was preceded by cutaneous tests to penicillin. A patch test with 200 units of amorphous commercial penicillin was placed on the right upper arm; both an intradermal and scratch test with 200 units of the same penicillin was done on the left forearm. All of these tests were entirely negative both in twenty minutes and in forty-eight hours.

Penicillin, in dosages of 50,000 units intramuscularly every three hours with amorphous commercial penicillin, was started on August 27, 1946. Atropine sulfate drops were used locally. There was no untoward reaction until after five days of penicillin therapy when a generalized erythema was noted. Twenty-four hours later a typical erythematous, generalized, maculopapular dermatitis appeared, almost explosively. Pruritus was intense and the rash most marked in the axillae, groins, and flexures of the elbows. At this time the patient's eye had shown much improvement. Penicillin therapy was discontinued, but not the treatment with atropine sulfate drops. A solution of sulfathiazole was also instilled into the affected eye. At the end of forty-eight hours the pruritus, erythema and rash had almost entirely receded.

A patch test with 200 units of crystalline penicillin G was done on the right upper arm. It was negative at the end of forty eight hours. An intradermal test with 2.5 units of crystalline penicillin G dissolved in 0.1 c.c. of normal saline produced an immediate erythema and edema with accentuation of the original injection wheal. There was a slightly elevated central edema; spreading pseudopodia appeared within twenty minutes and then receded in approximately one hour; an accentuation of this reaction was noted again in approximately six hours and persisted as a tuberculin-type reaction for the succeeding forty-eight hours. A control intradermal test with normal saline 0.1 c.c. was negative.

At the end of this time, the patient had an exacerbation of the keratoconjunctivitis, to which the response with topical sulfathiazole was unsatisfactory. Penicillin therapy was therefore resumed cautiously in the form of topical application of a solution containing 500 units per c.c. of amorphous penicillin in normal saline. This was instilled into the affected eye every three hours, and improvement followed for forty-eight hours. At that time, erythema, edema and vesiculation were noted on the periorbital region of the affected eye, over the cheek and extending to the areas of the face that had come in contact with the penicillin solution. A patch test on the arm was negative, but a patch test with 200 units of amorphous commercial penicillin on the angle of the right jaw gave a 2-plus reaction in twenty-four hours. A patch test of the left side of the face with the atropine eye drops was negative in twenty-four hours and remained so for the succeeding forty-eight hours. An intradermal test with sulfathiazole by Leftwich's method<sup>5</sup> was negative; patch testing of the upper arm and left face with sulfathiazole powder was negative. A repeated intradermal test with 200 units of amorphous commercial penicillin on the right forearm gave no immediate reaction and was negative at the end of forty-eight hours.

Two days later, a repeated patch test with 200 units of amorphous penicillin to the right face was negative at the end of forty-eight hours. At this stage of her illness an incidental coronary occlusion occurred. We felt that the results of the skin tests indicated a state of anergy to penicillin. Faced by the alternative of enucleation of the diseased eye under the handicap of her cardiac condition, it was decided to chance a resumption of penicillin therapy, which was given intramuscularly in dosages of 50,000 units of amorphous penicillin every three hours. The antibiotic was tolerated well for seven days, and resulted in rapid improvement in her eye condition. After several weeks of bed rest because of her coronary occlusion, she was discharged from the hospital free from symptoms of disease September 21, 1946.

A repeated intradermal test with 2.5 units of amorphous penicillin, using the same brand and lot that was used for her last course of therapy, thirty-one days after discharge gave an immediate reaginogenic type of reaction as well as a tuberculin-type reaction at the end of forty-eight hours. Repeated patch test with 200 units of the same amorphous penicillin gave a 2-plus reaction in forty-eight hours. Contact testing of the buccal mucous membrane<sup>2,3</sup> with 200 units of crystalline penicillin G showed a moderately positive reaction after one hour of contact. This persisted for twenty-four hours. Control contact tests were negative.

#### CONCLUSIONS

1. Patients under prolonged or repeated observation may show wide variations in the degree of hypersensitivity to penicillin.

2. The correlation of hypersensitivity reaction, cutaneous testing and penicillin therapy may be demonstrated.

3. Advantage may be taken from the demonstration of periods of relative anergy to penicillin for therapeutic action. It is obvious that the unavoidable risk involved will justify such procedure only in grave emergencies.

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#### DR. MORRIS FISHBEIN TO GIVE COURSE IN MEDICAL WRITING

Dr. Morris Fishbein, Editor of the *J.A.M.A.*, will give an instructional course in medical writing at the next annual meeting of the Mississippi Valley Medical Editors' Association, to be held at Springfield, Illinois, next September 29 during the annual meeting of the Mississippi Valley Medical Society in that city. No registration fee will be charged to members of the Association.

The Medical Editors' Association is contemplating changes in both its constitution and name, as it is felt that the name "Editors" is entirely too restrictive, and the name Medical "Writers" or "Authors" Association would be more appropriate. While every medical editor is a medical writer, every medical writer is not a medical editor. Since the principal purpose of the Association is to improve medical writing, hundreds of physicians should be interested in the organization, as most progressive physicians write articles and are interested in any effort to improve medical literature.

All interested in knowing more about this non-profit organization, or attending the meeting next September, should communicate with the Secretary, Dr. Harold Swanberg, 209-224 W.C.U. Bldg., Quincy, Illinois.

## ALLERGY IN CHILDREN AS RELATED TO ALTITUDE

JULIA BAKER, M.D.  
Mexico City, Mexico

CERTAIN observations during the last seven years on children in Mexico City have led to the conviction that altitude *per se* plays a part in the initiation and severity of allergic reactions. The conclusion seems inescapable that allergic tendencies are unduly common and severe at the high altitude of Mexico City (7,325 feet) and appear frequently in children never noticeably afflicted with allergic tendencies at lower altitudes. The evidence is based on the study of a random sample of 500 children in Mexico City which gave allergic symptoms in 48 per cent. This supplements a previous random sample of 500 which gave allergic symptoms in 53 per cent.<sup>1</sup> Of the 1,000 there were 509 who had allergic symptoms. The study includes sixty-two children who lived part of the time in Mexico City and part of the time at lower altitudes and who showed more allergic symptoms while in Mexico City. Two of these cases have been previously discussed.<sup>2</sup> Charts on seven others are included in this paper. Experimental evidence on the effect of altitude on anaphylactic shock has been previously cited.<sup>1</sup>

That the conditions observed and here referred to are allergic manifestations is supported by the following evidence: (1) Symptoms of children previously proved in the U. S. to be allergic become much worse at the altitude of Mexico City. (2) Children with allergic family history or allergic siblings have shown more allergic symptoms in Mexico City than at lower altitudes. (3) Symptoms are definitely related to the ingestion of certain foods and abate when these foods are omitted from the diet. (4) The foods most commonly causing the reactions are eggs, milk, orange juice, chocolate and wheat, foods recorded as causing allergic reactions in the U. S. (5) The reactions are not a result of the character of the food in Mexico City since the symptoms are commonly related to ingestion of different brands of powdered and canned milk imported from the U. S., as well as imported chocolate, soy bean milk, et cetera. (6) That the reactions have not been the result of infections has been established by blood counts, stool examinations, cultures, et cetera. (7) The symptoms involve the skin, the gastrointestinal tract and the respiratory tract, as usually defined in allergic cases. (8) Reactions to altitudes are not affected by race. Of 140 Mexican children in the group of 500, seventy-two were allergic (50.1 per cent). The other 360 children were Americans, with a few Europeans. Of the group of 203 younger children from six months to five years of age, seventy were Mexican. Of these seventy Mexican children, thirty-seven had hives (50.3 per cent).

<sup>1</sup>Presented at the Third Annual Meeting of the American College of Allergists at Atlantic City, N. J., June, 1947.

## SYMPTOMS

*Skin.*—Hives are the most common and clear-cut symptom. They appear as red macules about 1 to 1.5 cm. in diameter with irregular outline, itch intensely, and often form small vesicles about 2 mm. in diameter. If scratched, scabs form and there may follow a pigmented scar lasting several weeks. They are usually located on the trunk but may also be present on the face and extremities. They occur in crops and are usually accompanied by gastrointestinal or respiratory symptoms. They are distinguished from insect bites occurring in Mexico City by their character and by history. Generalized urticaria, as distinguished from what I refer to as hives, and atopic dermatitis occur commonly but less frequently than hives.

*Gastrointestinal Symptoms.*—These are anorexia, nausea, vomiting, abdominal pain, loose and frequent evacuations. If these symptoms are definitely related on three occasions to the ingestion of certain foods and abate when these foods are omitted from the diet, if the symptoms are also accompanied by hives, and if the blood-count is not elevated, the case is recorded as allergic. If any aspect suggests a doubt, stool examinations and cultures are done.

*Respiratory Symptoms.*—These symptoms consist of asthma, rhinitis with pale mucous membrane and watery discharge lasting more than a week, and in some cases chronic cough with postnasal drip. Tuberculin tests and x-rays are done on these cases, and if the conditions clear up suddenly on removing certain foods or inhalants, or skin tests to inhalants are positive and these prove clinically to be the offenders, the cases are recorded as allergic.

The gastrointestinal symptoms and the respiratory symptoms require more careful study to establish them as allergic than do the skin manifestations. Since hives, generalized urticaria and atopic dermatitis are very common in the age group of six months to five years, and since these symptoms are sharply defined, I have selected from within this age group patients on whom the record is sufficiently long to establish any definite relation between diet and hives. There are 203 individuals thus selected from this age group. Of these, 104 (51 per cent) have had skin symptoms attributable to certain foods. In this group of 203 children, there were twelve cases of geographic tongue (5.9 per cent), and in the group of 500 children there were twenty-five cases (5 per cent).

The detail of some of these cases at high and low altitudes appears on the charts, arrangement of which is according to an article on "Charting and Symbols" by Dr. Abraham B. Schwartz, published in *Journal of Pediatrics*, October, 1946.

# ALLERGY RELATED TO ALTITUDE—BAKER

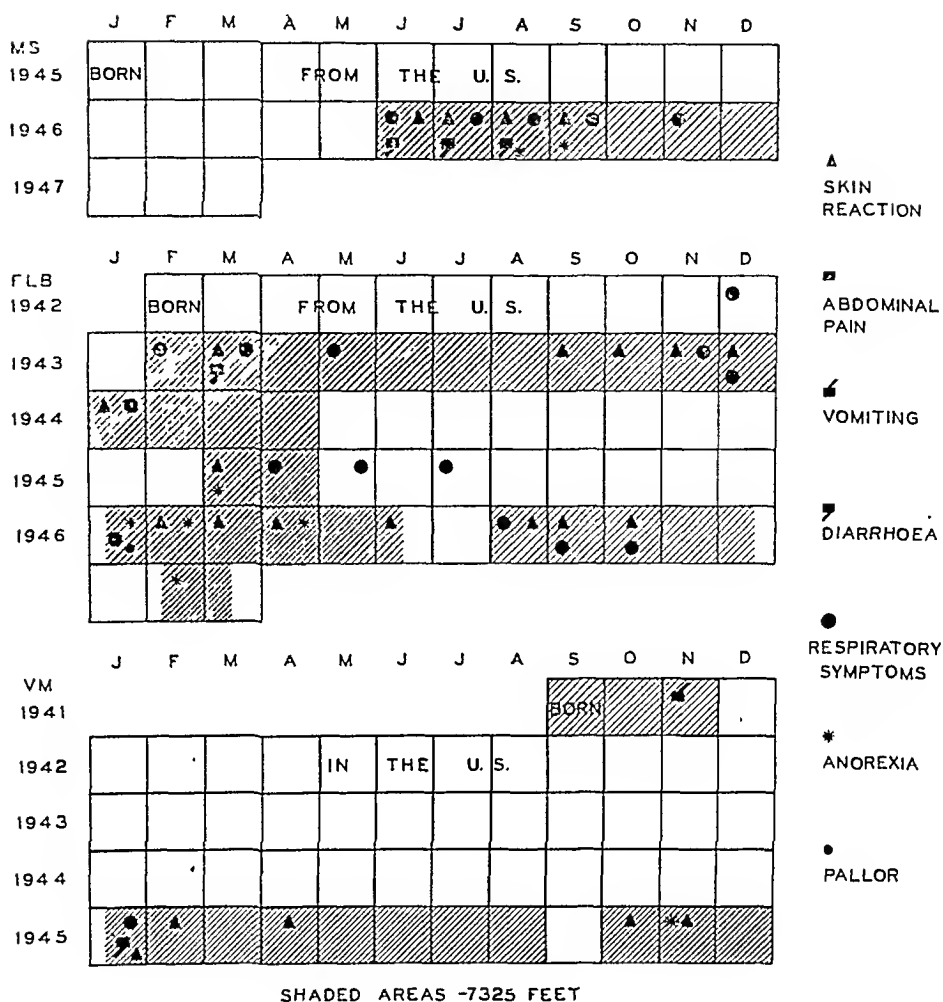


Chart I.

## DISCUSSION OF THE CHARTS

M.S. had never been ill before coming to Mexico. He had never had hives, colds, or loose bowel movements. He arrived in Mexico City in May, 1946, and immediately developed hives, loose bowel movements and running nose. All these lasted until July when he was first seen and put on a diet without milk, eggs or orange juice. His nose became better, bowel movements were reduced from five to two a day and no new hives appeared. On August 29 milk was given. He broke out in hives and his nose began to run, so milk was discontinued. On September 20 milk was begun again gradually, but he broke out in a rash. Milk was discontinued. October was uneventful. On November 8 he began to have a chronically running nose, but as skin and gastrointestinal tract were normal no further limitations were put on the diet. In December, 1946, he returned to Barberton, Ohio. A letter from his mother dated March 17, 1947, stated that he could eat everything including eggs, milk, and orange juice, and that he had no hives, rashes, running nose or loose bowel movements in the U. S. Another communication on May 20 stated that he was still symptom-free on a full diet.



F. L. B. had no allergic history and had been well from birth except for a respiratory infection in December, 1942. At the age of one year she arrived in Mexico City, on February 11, 1943. She developed a running nose, and in March, eczema. Eggs were recorded as disagreeing with her on several occasions. The eczema in March was accompanied by loose bowel movements and a running nose. With some dietary restrictions she became better and was free of skin symptoms until September when she developed hives. The hives recurred during October, November, December and January. In May, 1944, she went to the U. S. and stayed until March, 1945. On arrival in Mexico City, she developed generalized rash and anorexia, but improved on limiting the diet. In May, 1945, she went to the U. S. and stayed until January, 1946, where she was again free of symptoms. At this time she could eat chocolate with no ill effects, though if she ate it in Mexico City she developed hives. From January, 1946, through July she had hives frequently. In June and July, 1946, she spent six weeks in the U. S. and ate everything without reactions, but immediately on her return to Mexico City she developed hives and a running nose, both of which conditions lasted three months. On omitting wheat from the diet, these symptoms cleared up. On December 7, 1946, she went to the U. S. and stayed until February 7. While there she took eggs, milk, orange juice and wheat, and had no hives or running nose.

V. M. was born in Mexico City in September, 1941, and in November she began to vomit frequently. She went to Boston on December 1, 1941, and had no more vomiting. Her stay in the U. S. was prolonged and she had good health. Her mother asserts positively that she had no hives or gastrointestinal disturbances. She came to Mexico City in January, 1945, at the age of three and one-half years. On arrival she developed hives, loose bowel movements and running nose. The hives became severe in April, and were alleviated by reducing milk. She went to El Paso, Texas, for one month in September, 1945, and was very well, had an excellent appetite, and could eat eggs and drink orange juice there without getting hives. She cannot take eggs and orange juice in Mexico City. On returning to Mexico City in October, she broke out with hives and lost her appetite.

### *Chart II*

C. S. arrived in Mexico City on April 30, 1946. He had been completely well during the sixteen months of his life. On arrival he developed hives, anorexia and three to six loose bowel movements a day. The bowel movements became normal on omitting milk. Powdered milk was later begun very gradually, but he developed loose bowel movements. The family returned to the U. S. on July 28, 1946, because the child could not tolerate milk in Mexico City.

B. J. F. was born in March, 1945, and lived in the U. S. until February, 1946, during which time she had a good appetite, clear skin, normal bowel movements and no illness of any kind. She arrived in Mexico City on February 1, 1946, and developed an atopic dermatitis on her cheeks, and anorexia. Omitting eggs and orange juice relieved the anorexia. In June, 1946, loose bowel movements were corrected by omitting milk from the diet. Later evaporated milk imported from the U. S. was begun gradually, but on October 4, 1946, she developed loose bowel movements, anorexia and extreme pallor. On omitting milk these symptoms disappeared. Milk was omitted from October 4 until November 7. During the month from November 7 to December 6, she took daily one cup of diluted evaporated milk imported from the U. S., and lost weight, so it was again omitted, and from December 6 to January 6, 1947, she gained weight.

C. F. was born in February, 1943, lived uneventfully in the U. S. with no hives or illness of any sort until arriving in Mexico City in December, 1944, whereupon he broke out in hives that lasted for three weeks. At the same time he developed

# ALLERGY RELATED TO ALTITUDE—BAKER

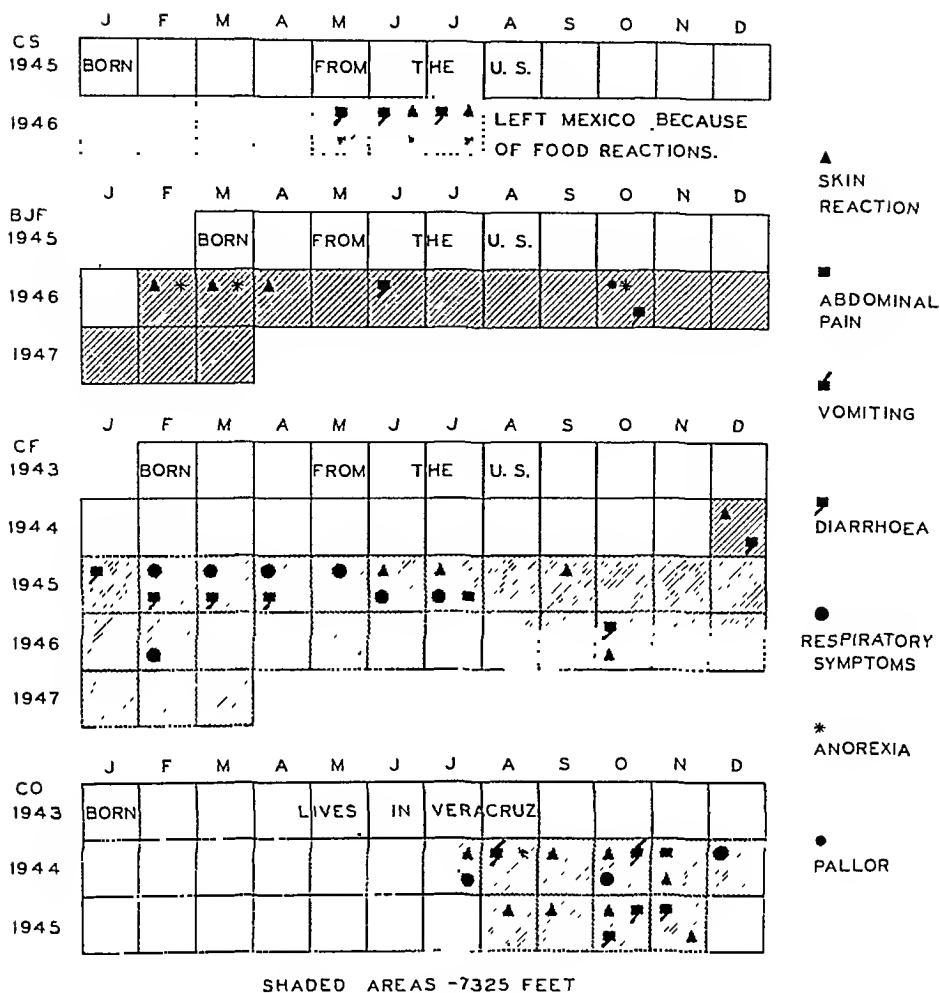


Chart II.

loose bowel movements, three to four a day, and this lasted through December, January, February, March, and April. During this same period, he developed a chronically running nose which lasted from February to July. When his diet was limited over short periods, improvement in the symptoms was noted, but this was done only sporadically, and for a short time following acute episodes. He went to the U. S. in July, 1946, and was very well, with improved appetite. On his return to Mexico City, he had no trouble until October when he developed hives and loose bowel movements, which were controlled by diet.

C. O. was born in January, 1943, and lived at sea level in Veraeruz, Mexico. He came to Mexico City July 25, 1944. On August 4 he developed loose bowel movements, three times a day, and on August 7 began to vomit everything so that he became acidotic and had to have intravenous Hartman's solution. On a limited diet he improved. He was still getting milk, but this was omitted later, on December 15, because of constantly running nose. The condition improved with this limitation of diet. However, all during his five months' stay in Mexico City he had symptoms related to the gastrointestinal tract, the skin, and the respiratory system (as seen on the chart), although not so severe as on arrival. He was in Veraeruz a year, where

he had no trouble, and returned to Mexico City in August, 1945. It was definitely recorded at this time that eggs and chocolate caused him to have loose bowel movements and hives in Mexico City but not in Veracruz. He had hives all during his stay in Mexico City in 1945. He was never known to have hives in Veracruz.

I shall discuss one more case although it does not appear on the charts. L. S. was born in the U. S. in April, 1943. Soon after birth she developed vomiting, a symptom evident for one year and assigned as allergic by her physician. Pabulum, egg, apricot and apple caused vomiting and hives. At one year the vomiting stopped, but she had abdominal pain and gas, always relieved by enema and definitely related to certain foods. At two years she began to improve, and at two and a half years she could eat all foods. At two years and eight months she came to Mexico City. On a full diet she had minor allergic symptoms for two months, and in February, 1946, two months after arrival, she developed severe allergy with sneezing, running nose, severe abdominal pain, anorexia and hives. According to her mother, the time in Mexico City was the worst period of her life in regard to allergy, and her symptoms were kept under control only by a diet without milk, orange juice, egg, apricot and wheat. She went to West Point in April, 1946, and improved immediately. She was free from abdominal pain and began to gain weight. She was able to take milk and wheat without trouble, but a letter from her mother in January, 1947, stated that she was still unable to tolerate orange juice.

#### SUMMARY

Of 1,000 children seen in general pediatrics practice, 509 have shown definite allergic symptoms in Mexico City at an altitude of 7,325. Sixty-two children who lived part of the time in Mexico City and part of the time at lower altitudes were free of these allergic symptoms at the lower altitudes, or the symptoms were less severe there. Charts of seven of these cases are shown.

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# SYMPTOMATIC PURPURA OCCURRING WITH MALARIA

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**O**BSERVATIONS made on a male veteran of World War II during the course of his first clinically recognized attack of malaria are described herein. The significance of the report resides in the fact that approximately two weeks after the onset of an undiagnosed illness, characterized by chills and fever and later proved to be malaria, this man developed petechial hemorrhages in the conjunctiva of both eyes and in the mucous membrane covering the palate.

All of the textbook descriptions of malaria do not mention purpura as a manifestation of the disease. Shrager and Kean<sup>2</sup> found, however, in reviewing the literature on the subject, that various hemorrhagic manifestations (petechiae, ecchymosis, epistaxis, and hemoglobinuria) have been described. These were said to have occurred usually in early pernicious cases of malaria and occasionally in the chronic forms of the disease. They also reported ten new cases of purpura found among 10,000 consecutive patients with malaria seen at the Gorgas Hospital. Four of the patients were placed on the seriously ill list because of the purpura, and two died. Nine of the ten cases developed purpura following the administration of quinine, and it is perhaps not unreasonable to assume that this played a role in the genesis of the condition. However, since the cases were not tested for sensitivity to quinine, and since various studies have suggested that malarial parasites and quinine in combination may occasionally produce such an effect, the exact etiology of the lesions observed in their cases remains in doubt.

Allergic manifestations other than purpura, considered due to the sensitivity of the human host to the infecting malarial organism, are likewise seldom seen, but do occur.<sup>1</sup>

Since reported instances of purpura associated with malaria are rare, and since the clinical finding could readily lead to an erroneous diagnosis of bacteremia, a report seems appropriate.

## CASE REPORT

A thirty-year-old veteran (J.F.J.), employed as a butcher, was admitted to the hospital on December 26, 1946, complaining of recurrent "fever and chills". The attacks had begun about two weeks prior to admission and had occurred practically every other day. They were usually accompanied by severe headache, backache, and pains in the muscles and joints. During the intervals between the

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(The opinions set forth in this article are those of the writers and are not to be construed as necessarily reflecting the policies of the Navy Department.)

paroxysms the patient felt fairly well. Several days following the onset of his illness, he had consulted a physician who had prescribed sulfadiazine, 1 Gm. every four hours for four doses. One week before entering the hospital the patient had been given quinine sulfate, 5 gr. for three doses. Neither of these drugs had appreciably influenced his symptoms.

A review of the patient's past history revealed that in 1944 and 1945 he had been stationed in the Southwest Pacific on New Guinea and Leyte. He had taken suppressive dose of atabrine from the time he entered the above-mentioned areas until he returned to the United States in 1945, and did not develop clinical malaria prior to the onset of his present illness.

Physical examination at the time of admission revealed a well-developed, rather obese white man who appeared acutely ill. The temperature was 102° F. and the pulse rate was 134. The blood pressure was 100/74. There was no skin erythema. The eyes showed bilateral subconjunctival hemorrhages. There were a number of pinpoint hemorrhages present in the soft palate. There were no heart murmurs, and the lungs were clear to auscultation and percussion. The liver and spleen were not enlarged to palpation and percussion.

The admission diagnosis was "probable septicemia."

*Laboratory Findings.*—The red blood cell count was 4,800,000; the hemoglobin was 14.5 grams (Haden-Hausser), and the leukocyte count was 10,200. The differential count was 56 polymorphonuclear cells, 36 lymphocytes, 3 eosinophiles, 1 basophile and 4 monocytes. The bleeding time (Duke) was 4 minutes, and the clotting time was 2½ minutes. The platelet count was 264,000. The prothrombin time was 19 seconds (control—17 seconds). A thin blood smear was positive for *Plasmodium vivax*. Early ring forms and infected erythrocytes containing Schüffner's dots were observed in moderate numbers. The Kahn test was negative. The urinalysis was normal. Blood cultures using tryptose phosphate broth and Brewer's medium were negative at the end of two weeks.

*Treatment and Course.*—After the diagnosis of malaria was established, the patient was given atabrine, 3 gr. every six hours. Within twenty-four hours after the institution of therapy, the subconjunctival hemorrhages had begun to fade. The hemorrhages in the soft palate, however, showed no change. After a week the petechiae in the soft palate had disappeared; only faint traces of the subconjunctival hemorrhages remained, and the patient felt well except for some "nervousness."

In an attempt to determine the sensitivity of the patient to quinine, a scratch test using a 1:10 dilution of quinine sulfate was done seventeen days following the first ingestion of quinine. The reaction to this was negative. Feinberg<sup>3</sup> states that quinine is unlike many of the simple drugs, in that positive scratch reactions may occur in patients sensitive to this drug.

Three 5-grain capsules of quinine sulfate were given to the patient following the scratch test in an effort to determine whether this would elicit any allergic phenomena. Purpuric manifestations failed to develop following the ingestion of this drug.

The patient was also given 1 Gm. of sulfadiazine four times a day for two days to rule it out as a possible cause of the purpura. No purpura developed following the administration of sulfadiazine.

The patient was seen seven months after he left the hospital and had had no further purpuric manifestations.

# SYMPTOMATIC PURPURA—NELSON AND BLACK

## DISCUSSION

It has been shown<sup>2</sup> that urticaria is not uncommon following the administration of quinine. In this regard, the postulation of Quick<sup>4</sup> is interesting, in that he predicates that the release of histamine is the basic cause of both simple urticaria and thrombocytopenic purpura and the difference in the two is merely quantitative.

This case represents a patient who developed purpuric manifestations during an infection with *Plasmodium vivax*. The role of the quinine in the genesis of the purpura is not clear. However, the negative scratch test to quinine sulfate and the failure to develop purpuric manifestations following test doses of quinine indicate that the purpura was probably due to the malarial infection.

## SUMMARY

A case of malaria with symptomatic purpura is described. A partial review of the literature and a brief discussion of the significance of this manifestation are presented.

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# THE USE OF MICRONIZED THERAPEUTIC AGENTS BY INHALATION

## With Special Reference to Allergic Pulmonary Conditions

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**I**N our preliminary report we described a method of administering by inhalation various finely divided, solid therapeutic agents suspended in air.

To an allergist, dusts have always meant trouble; however, dusts do have some properties which are quite interesting. It has been known for a considerable time that the particle size of various dusts plays a very important role in the toxicology of the dust. For example, dusts of silicon dioxide with particle sizes above 10 to 15 microns usually fail to reach the alveoli of the lung and thus do not play an important part as a causative factor of silicosis; however, particles ranging around 1 micron do reach the alveoli, and considerable numbers of them remain in the alveoli for a long enough period to produce the reactions noted in silicosis. Particles which are considerably finer than 1 micron have a tendency to be expelled from the alveoli and the respiratory tree with the exhaled breath. If a soluble compound is considered in the form of a dust, we feel that the most efficacious particle size for that dust to be absorbed from the lungs is approximately 1 micron. Therefore, we have produced our finely divided penicillin-glucose mixtures with a mean particle size range of 1 micron. Light microscope and electron microscope studies of the particle size distribution of our preparation show that the mean particle size ranges around 1 micron, greatest longitudinal dimension.

Administration of micronized therapeutic agents to animals by inhalation has been performed. Histological sections of the respiratory tract made at various intervals after administration have shown no abnormalities.

So far, the utilization of any solid dry therapeutic agent, which is not gummy or elastic in nature, has presented no difficulties in preparation for use by this method. It would be safe to say that the limiting factors in the use of any solid therapeutic agent by this method would be the absorbability by the respiratory tree and the pharmacological properties of the agent.

To maintain the potency of penicillin, it is necessary to keep the preparation dry. This also prevents agglomeration of the fine dust particles. Therefore, in the preparation of our materials we find that dryness and fine particle size are of utmost importance.

### THE APPARATUS

The equipment for producing the suspension of fine particles in air is comparatively simple, and on repeated tests has proven to be most

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Work performed at the University of Rochester School of Medicine and Dentistry, in the Departments of Medicine and Radiology, under a grant-in-aid from the Lederle Laboratories Division of American Cyanamid Company.

efficient.<sup>4</sup> At present, there are two types of equipment, one consists of a 1-inch diameter plastic tube, approximately 4 inches long, which is divided into two chambers—an upper chamber where the finely divided

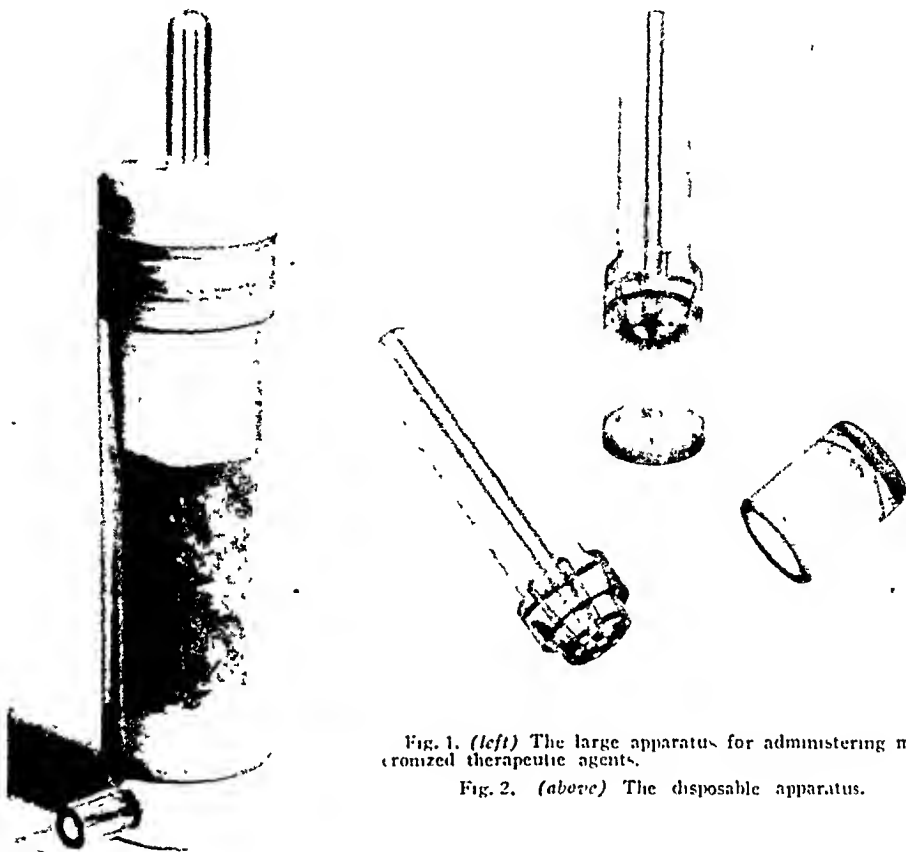


Fig. 1. (left) The large apparatus for administering micronized therapeutic agents.

Fig. 2. (above) The disposable apparatus.

therapeutic agent is placed, and a lower chamber which contains a dehydrating agent for drying the air to be passed over the therapeutic agent. This apparatus requires air pressure from a standard rubber bulb (Fig. 1).

The second piece of equipment is much smaller and does not require the use of a rubber bulb. It consists of a solid upper portion, approximately 2 inches long and shaped to fit either into a nostril or into the mouth. This portion contains the outlet vent and the inlet orifices for producing the air turbulence which in turn produces the suspension of the therapeutic agent. This apparatus is fitted with a small cup which attaches to the base. This cup acts as the container and also is an hermetically sealed dispenser of measured amounts of the therapeutic agent. Therefore, no dehydrating agent is necessary with his apparatus (Fig. 2).

In practice, the first piece of equipment described is used in the following manner: The top cap is unscrewed, and a capsule containing a measured



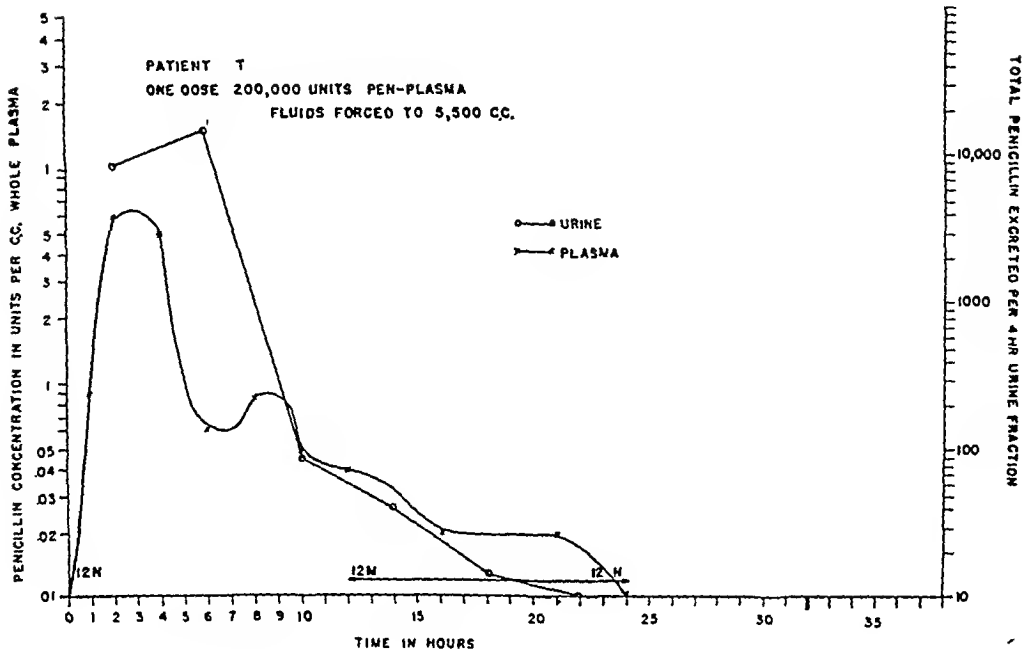


Fig. 3.

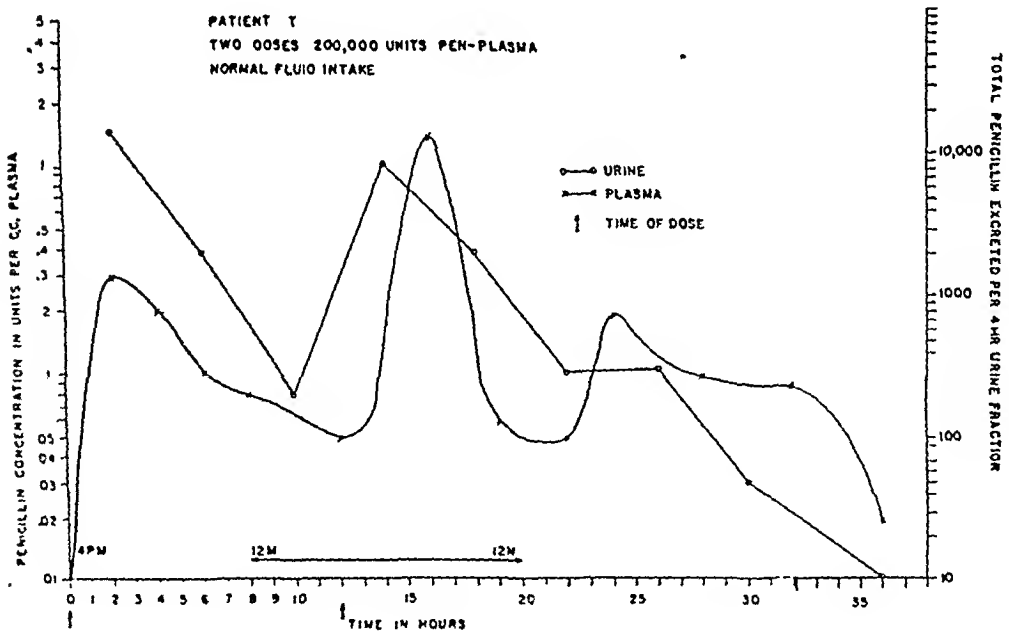


Fig. 4.

amount of the finely ground therapeutic agent or agents, either with or without a vehicle such as glucose, is emptied into the upper chamber. The cap is then replaced and the equipment held so that the outlet tube is slightly within the partially opened mouth. The patient first exhales deeply and then takes a slow, long inspiration. During the period of inspiration, the

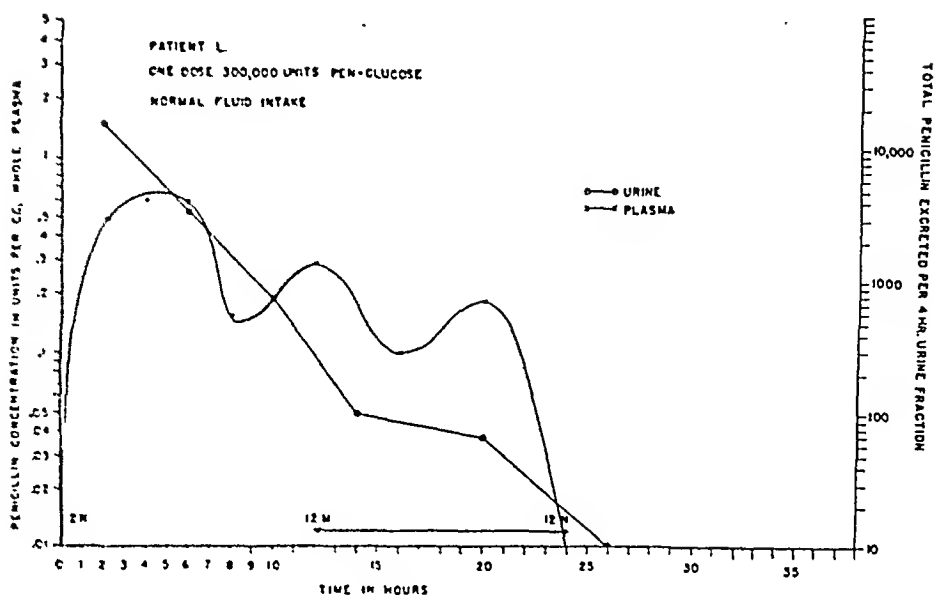


Fig. 5.

rubber bulb is compressed with rapid, light strokes. Heavy compression of the bulb produces a very dense suspension and might cause coughing. At the end of the period of inspiration, the patient stops compressing the bulb, holds the breath for a few seconds, then exhales through the nose and repeats the procedure until the therapeutic agent is entirely used—which takes approximately three minutes.

In the small disposable type of apparatus, the solid upper portion is held in the hand and the small cup-like container is uncapped and screwed onto the delivery tube portion. In some of our models, the cup is attached to the delivery tube portion by means of a press fit. The patient then exhales deeply, inserts the delivery tube either into the mouth or into one nostril, and then inspires slowly and deeply. This procedure is repeated until the therapeutic agent is completely gone from the cup. It is important that the patient does not exhale or blow back into the apparatus.

#### PENICILLIN

The first agent studied was crystallin potassium penicillin. To prove its effectiveness by this route, it was necessary to determine its rate of absorption and excretion. At first this was done using protocols described by Segal et al<sup>3</sup> for aerosol penicillin. Soon it was found that the blood concentrations were higher and more sustained than those recorded after inhalation of mist type penicillin aerosols by several investigators. A serial dilution method of penicillin assay was used<sup>2</sup> and found cumbersome, tedious, and difficult to reduplicate. By modification of Forgaç's method<sup>1</sup> for streptomycin assay, we developed a method of penicillin assay which is simple and ac-

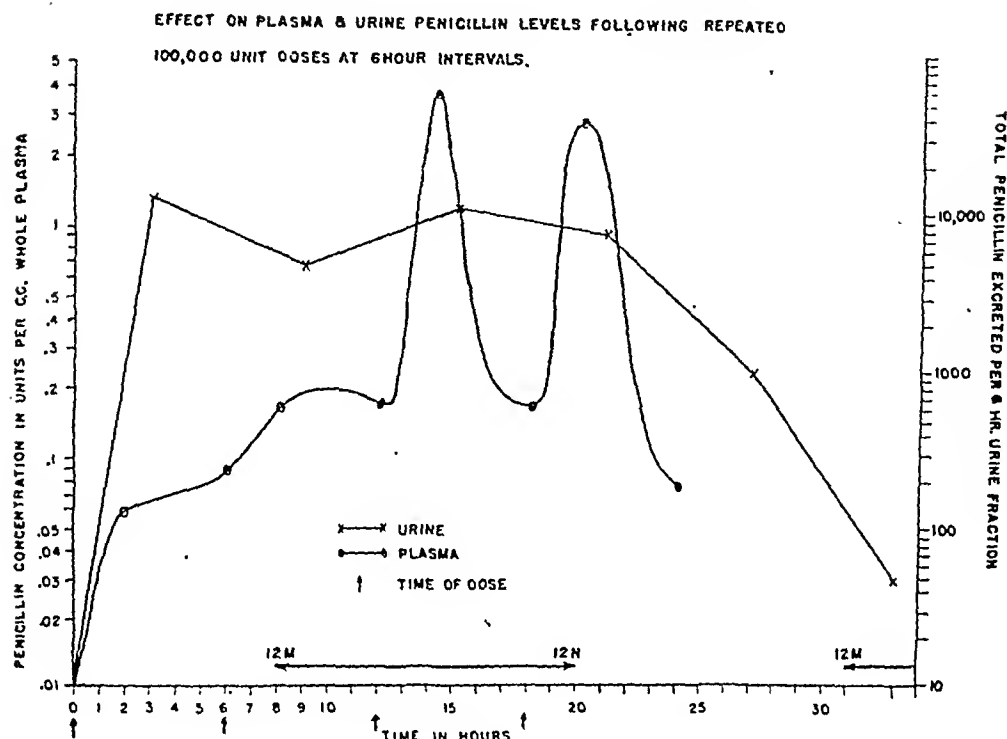


Fig. 6.

curate. With this method, fifty specimens may be prepared for analysis in two hours, and the penicillin concentrations read after four hours incubation at  $39.5^{\circ}\text{C}$ . Since this is a micro method, only ear lobe or finger tip blood specimens are necessary. The blood and urine penicillin concentrations following varying doses are shown in Figures 3-6.

Before using penicillin on patients, it was decided to add an antihistamine substance to the mixture, to decrease the chance of severe allergic pulmonary reactions. One per cent powdered Benadryl was used because it had a less disagreeable odor than other antihistamine substances. Analysis of 320 patients treated is shown in Table I.

#### CLINICAL RESPONSE TO PENICILLIN TREATMENT OF INTRINSIC BRONCHIAL ASTHMA AND RELATED BRONCHIAL DISEASE

The fifty patients in this group responded in a similar manner to that described by many others who used inhalations of aerosol penicillin. We have been able to evaluate the temporary benefit only, since none of our cases have been followed longer than four months. We can say that penicillin-sensitive organisms are nearly always eliminated from the throat and sputum in a few days and in the majority of instances are replaced by coli-form organisms. Such organisms in the respiratory tract act as saprophytes. They persist for two to three weeks after treatment has been discontinued. Practically all bacteria may be removed from the respiratory tract temporarily by using mixtures of penicillin and streptomycin.

# MICRONIZED THERAPEUTIC AGENTS—TAPLIN AND BRYAN

TABLE 1. ANALYSIS OF PENICILLIN REACTIONS

1. Gross incidence of allergic reactions in 320 cases = 18 = 5.6%.
2. Gross incidence of local allergic reactions† in 320 cases = 15 = 4.7%.
3. Gross incidence of general allergic reactions\* in 320 cases = 3 = 0.94%.
4. Incidence of previous allergic state among patients developing penicillin sensitivity. 18 cases sensitized, 11 cases with evidence of previous allergic state = 61%.
5. Gross incidence of local allergic reactions in 51 cases of chronic pulmonary disease = 11 = 21.5%.
6. Gross incidence of general allergic reactions in 51 cases of chronic pulmonary disease = 1 = 2%.
7. Average time of appearance of local allergic reactions after start of treatment is 8 to 10 days. Earliest at 4 days, and latest at 14 days.

†Local allergic reaction consists of any one or combination of the following: Soreness, redness, swelling or occasional vesicle formation of the pharynx, tongue or larynx.

\*General allergic reaction consists of urticaria, arthralgia, flare-up of pre-existing epidermophytosis, angioneurotic edema, pulmonary edema or asthma.

Clinically, the favorable response reported by patients is the reduction in cough and decrease in amount of sputum production and relief of asthma in many cases. Seven to fourteen days of penicillin or penicillin-streptomycin therapy produces a remission for a period of one to eight weeks in most cases. The daily dosage varied from 50,000 to 200,000 units per day, given in divided doses two to six times a day.

Micronized Benadryl used alone or mixed with vasoconstrictors, such as Neosynephrine or Propadrine, have been found to be effective symptomatically in asthma and should be useful in hay fever. Several patients have obtained relief in five to fifteen minutes; the relief lasted one to eight hours after one inhalation of 1/20 to 1/10 the usual oral dose. This relief is associated with an increase of vital capacity from 100 to 500 c.c.

We have just begun to explore the effect of inhaling various micronized antihistamines, vasoconstrictors, and powdered cough mixtures. The preliminary results have been better than anticipated.

## DISCUSSION

There have been no definite allergic pulmonary reactions to penicillin, such as asthma, pulmonary edema or anaphylactic reaction. We have seen approximately 5 per cent allergic sore throats, characterized by redness, swelling, and occasionally, vesicle formation, mainly in atopic individuals. This local allergic reaction usually appears after four to fourteen days of continuous treatment, and subsides in two to five days when penicillin is discontinued and moderate doses of antihistamine are given by mouth or applied locally. If penicillin is readministered to such patients after a period of two to eight weeks, the same reaction is likely to appear, but its onset is sooner than after the initial course of treatment. Even in these cases, no allergic pulmonary reactions were encountered. In a series subsequent to the 320 cases here reported, it has been found that by instructing patients to take a few swallows of water immediately following each treatment, the incidence of local allergic sore throat reaction is greatly reduced. We attribute this effect to the removal of the high concentration of penicillin from the throat. This removal of the penicillin reduces the possibility of its causing an irritation or allergic reaction.

We have seen the usual serum disease-like reactions to penicillin in slightly less than 1 per cent of the total cases, consisting of urticaria, arthralgia, and general malaise. In one case, it was possible to desensitize the patient by daily inhalations of small amounts of penicillin. Another allergic manifestation seen was the exacerbation of pre-existing fungus infection of the feet and hands. This reaction did not preclude the continued administration of penicillin when the local infection was treated simultaneously with a fungicidal ointment and antihistamine substance by mouth. In two patients, a moderately severe angioneurotic edema of the lips and face occurred, associated with a sore throat reaction. Both reactions subsided readily on antihistamine substance by mouth. Sore, red tongue appeared in some patients treated for more than ten days. The tongue had the appearance of vitamin B deficiency, and responded to treatment with liver and vitamin B complex intramuscularly.

## SUMMARY

1. Micronized potassium penicillin, mixed with 1 per cent Benadryl plus a vehicle of glucose or blood plasma, has been used in 320 cases.
2. A 4.7 per cent incidence of allergic sore throat reactions and 0.9 per cent rate of generalized sensitivity reaction has been observed.
3. There have been no definite pulmonary reactions of allergic nature.
4. This method of giving antibiotics is particularly efficacious in diseases of the respiratory tract and can be self-administered effectively and painlessly.
5. Micronized Benadryl drugs alone or in combination with vasoconstrictors give symptomatic relief in asthma.
6. This method is simple, economical, self-administered, eliminates injection, and is preferred to injection by the majority of patients.

ADDENDUM: Subsequent work has shown that the use of finger tip blood often shows false positive B. Subtilis inhibition, probably due to hemolysis and tissue juices. Further, Sodium Penicillin preparations, in comparable doses are much more rapidly absorbed and excreted.

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# **Southeastern Allergy Association**

**Meeting of January 18-19, 1947**

Papers presented at the second annual meeting of the Southeastern Allergy Association held in Atlanta, Georgia, January 18 and 19, 1947, are published here in abstract form as a record of the proceedings of the Association.

The paper entitled "Allergic Problems of the Gastrointestinal Tract," by J. A. Rudolph, M.D., and Charles V. Sage, M.D., is published in full elsewhere in this issue.

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## **DIFFERENTIAL DIAGNOSIS OF ALLERGY AND INFECTION IN RELATION TO THE PARANASAL SINUSES**

**RALPH V. ELLIS, M.D., F.A.C.A.**  
**Greensboro, North Carolina**

THE frequency with which allergic inflammation of the paranasal sinuses is confused with infection in these areas is stressed: The large amount of needless surgery done without benefit upon allergic sinuses is deprecated. Criteria for the differential diagnosis of allergy and infection relative to the paranasal sinuses, including data obtained by inspection of the nasal cavities, cytological studies of nasal smears, roentgenograms and erythrocyte sedimentation rates, are reviewed.

These criteria were applied to 100 consecutive patients with nasal complaints seen in the Eye, Ear, Nose and Throat Clinic of the Students Health Service at the University of Minnesota. Thirty-one (31 per cent) of the series presented cloudiness of the antra by x-ray, yet in only eleven of these was infection demonstrable. The sedimentation rate was elevated in all for whom infection was proved. The sedimentation rate done by the Westergren method was arbitrarily adjudged slow when less than 5 mm. for one hour. Seventy (70 per cent) of the 100 cases by this standard had slow rates, and, of these, sixty-eight were demonstrably allergic. Sixteen patients had cloudiness of the antra and slow sedimentation rates. All of these proved to be allergic and without infection.

It is concluded that the erythrocytes sedimentation rate furnishes information of greatest value in differential diagnosis of allergy and infection of the paranasal sinuses.

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## **SIGNIFICANCE OF SKIN TESTS IN SUSPECTED DRUG SENSITIVITY**

**O. C. HANSEN-PRUSS, M.D., F.A.C.A., and W. E. LEEPER, JR., M.D.**  
**Durham, North Carolina**

THE failure of any single method of testing to prove applicable in all types of drug hypersensitivity has caused many physicians to abandon all forms of testing for sensitivity to simple chemicals. The cause for this pessimism, and its remedy, will be found in a careful analysis of the na-

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From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

ture of drug allergy. The distinguishing feature of this form of hypersensitivity is the character of the antigen. Being nonprotein, these simple substances must combine with protein to become antigenic. The second peculiarity is comparable to that attaining in food allergy. The drug is often administered by mouth and is subject to the processes of digestion, absorption, and metabolism. These processes may alter the nature of the antigen so that it (in its final active form) may differ greatly from the pure drug. This may account for the frequent failure of methods of testing which utilize the pure drug. The third distinguishing feature is the apparently very low titers of specific antibody present in the circulating blood. If these peculiarities of drug allergy are taken into consideration, more or less standard techniques can be selected for its demonstration.

The patch test is often positive in the cutaneous forms of drug allergy and, in particular, in arsenical sensitivity. It is specific in contact sensitivities. False positive reactions are caused by the primary toxicity of the compound.

The intradermal test is comparable to the patch test but of less value.

The application of the suspected substance to the tongue or buccal mucous membranes may result in local or systemic reactions of diagnostic significance.

The conjunctival test is especially valuable in determining diodrast sensitivity.

The leukopenic index following oral administration of drug may be of value but has not received a careful trial.

Readministration of the drug is the method of choice whenever the allergic disorder is not of such severity as to endanger life or threaten permanent damage. For demonstrating sensitivity to the coal tar derivatives, mixtures of the pure drug and human serum often produce a typical erythema and wheal when injected intradermally. Presumably these mixtures contain a drug-protein combination which acts as an antigen.

Leftwich's basic work on sulfonamide sensitivity has shown that the serum of individuals receiving these drugs in therapeutic amounts for five or more days contains an antigen which produces a positive intradermal reaction in individuals sensitive to these drugs.

The usual passive transfer test is of little or no value in drug allergy. The reverse technique of administering the antigen by mouth after preparing the skin with the serum of a sensitive individual will often detect very low antibody titers and may, therefore, be useful in the study of drug allergy.

It is believed that a careful analysis of each case will indicate which of these methods or which modifications of these methods will prove applicable to that case and that it will often be possible to identify the responsible drug.

**BRONCHIAL ASTHMA — DIFFERENTIAL DIAGNOSIS**

**Report of Two Cases of Bullous Emphysema**

MASON I. LOWANCE, M.D., F.A.C.A., EUGENIA C. JONES, M.D., WARREN B. MATTHEWS, M.D., and EDGAR M. DUNSTAN, M.D.

Atlanta, Georgia

**F**IVE cases are presented, illustrating typical diagnostic problems encountered in the study of bronchial asthma. Two cases present the picture of bullous emphysema. In one case, this was unilateral; in the other, it was bilateral and also accompanied by the presence of pulmonary tuberculosis. One case presented bronchial asthma with subsequent development of chest pain and a mass in the right chest.

Surgical interference demonstrated a mass of omentum herniated through the anterior epigastric foramen into the interlobar fissure between the right middle and lower lobes. One case presented a picture of bronchial asthma with a superimposed cardiac asthma, cardiac decompensation, and coronary occlusion. One presented the picture of carcinomatosis with onset of asthma a few years previously.

A review of six recent articles is presented.

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**X-RAY THERAPY AS AN ADJUNCT IN THE TREATMENT OF  
BRONCHIAL ASTHMA**

**Preliminary Report**

KATHERINE BAYLISS MACINNIS, M.D., F.A.C.A.  
Columbia, South Carolina

**A** REVIEW of the literature reveals that x-ray therapy has been used for the relief of bronchial asthma for a number of years. Most of the patients treated have been classed as having severe attacks of asthma for long periods of time. Treatments have not been directed to just one area of the body, but have included the sinuses, chest, spleen, thyroid, pancreas, liver, adrenals and cervical sympathetics, with equally good results obtained. Relief has been noted in 40 to 75 per cent of cases treated.

We have run a small series of cases on children, giving them treatments every five days for four exposures. This was then followed by one exposure every month for four months. The results have been most remarkable in 75 per cent of the cases. X-ray films at the end of six months show considerable improvement over those taken just prior to beginning the treatments. These pathological findings as presented in the slides substantiate the clinical observations.



## THE ALLERGIC CHILD

W. L. RUCKS, M.D., F.A.C.A. (Assoc.)  
Memphis, Tennessee

THE early diagnosis and institution of proper treatment of allergy in infants might prevent many serious emotional and physical handicaps in later life.

Every physician should recognize the allergic significance of colic, food and formula disagreement, regurgitation, repeated upper respiratory infections and dermatoses in infants; and, of no less importance, a family history of allergy.

Allergic symptoms may be so mild that the child can carry on without appreciable difficulty, or, following removal of tonsils and adenoids, the symptoms may be relieved for years, only to return subsequently. It is the chronic or untreated cases that lead to trouble in later years.

Some of the more common manifestations of allergy arise from functional imbalance of the autonomic nervous system, among them, allergic coryza, asthma, eczema, and diverse anaphylactic reactions. The location of the shock organs are considered responsible for the different types of reactions produced. Pharmacologic reactions which stimulate or depress the nervous system are of short duration. For the permanent relief of the patient, the causative allergen or allergens must be discovered and removed, or proper treatment must be instituted.

The effect of the autonomic nervous system on the acid-base balance is important, since children cannot withstand tendencies towards acidosis or alkalosis for an appreciable length of time. The early recognition of either of these symptom complexes and administration of necessary electrolytes to restore a proper balance may be life saving.

*Atopic Dermatitis (Eczema).*—Many cases of atopic dermatitis begin *in utero*, when the fetus becomes sensitized to foods eaten by the mother. Others are due to stock milk formulas. These children are allergic to a number of foods, to atmospheric changes, and a variety of contactants. The treatment is based upon correction of the diet, elimination of irritating contactants, prevention of infection and measures to make the patient comfortable. The mild forms respond to treatment readily, though the severe types tax the ingenuity of the physician.

*Sinusitis.*—The diagnosis of nasal allergy can be made from the history, the changes in the mucous membrane, roentgenograms of the sinuses, and the bacteriology and cytology of nasal and sinus secretions.

We have been particularly interested in the effect of infection and allergic reactions on sinus development. If ventilation and drainage are adequate, the sinuses develop normally. Further, sinus development follows a definite pattern at certain ages.

Sinus disease is often of allergic rather than infectious origin; in such cases, if conservative ventilation and drainage are accompanied by proper allergic treatment, development will proceed normally.

*Asthmatic Bronchitis.*—This condition presents a most difficult diagnostic problem. The history means more than the skin reactions. Every patient should have the most complete examination possible, and all infections which can initiate asthma should be ruled out.

The problem may be more difficult if the allergic condition is associated with some other type of chest disease. Case reviews illustrating some of these diagnostic problems are presented.

The treatment is an individual problem. It should include immunization against contagious and respiratory affections.

Educational programs for the medical profession, medical students and laity in the early recognition and treatment of the allergic child will give to this country fewer physically and emotionally handicapped adults. These programs are vitally important if allergy is to take its place in preventive medicine.

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## THE MEDICAL MANAGEMENT OF ATTACKS OF BRONCHIAL ASTHMA

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THE management of attacks of bronchial asthma is usually both immunologic and therapeutic. The immunologic measures include the identification, by history or by test, of the specific eliciting agents, and their removal or avoidance. Where such procedures are unsuccessful, immunizing hypodermic injections of the specific agents are given. However, this discussion is not concerned with these procedures but rather with the therapeutic measures found necessary.

Attacks of bronchial asthma may be (1) mild, (2) severe, (3) intractable. In the mild cases, usually reversible, with a fleeting edema of the bronchial mucosa as the chief pathologic feature, vasoconstrictor drugs are indicated, such as ephedrine and epinephrine, the former orally, the latter by injection or by nebulization. In the severe cases, such drugs also are indicated, but the secondary pathologic changes of hypertrophy of bronchial mucosa, with increased bronchial secretion, and often with bronchiectasis, require expectorant drugs, such as the iodides and ammonium chloride. Epinephrine in oil or in gelatin, to retard its rate of absorption, may be required. Oral, rectal or intravenous doses of aminophyllin are often helpful. Stramonium nitrite is often helpful. Codeine may be required for the excessive cough. X-ray therapy is useful in some cases, but heat

therapy seldom. Purgation, semi-starvation, and bed rest are valuable adjuncts.

In the intractable cases, in addition to these measures, oxygen by catheter or by mask or tent is required. Helium may be added. Ether in oil, rectally, may help. Glucose or glucose saline, intravenously, will combat dehydration. Demerol is useful. The antihistaminic drugs aid in a few cases. Sulfonamides and penicillin infrequently aid in bacterial cases by combating the infection.

Drugs to be used with caution, if at all, are atropine or belladonna, which dry the bronchial secretions; morphine, which suppresses the cough reflex or the respiratory center, and aspirin (with other coal tar drugs), to which occasional patients are violently allergic.

Drugs of little or no value in the treatment of bronchial asthma are calcium, potassium chloride, histamine and histaminase.

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## PULMONARY TUBERCULOSIS AND ALLERGIC ASTHMA

NORMAN VAN WEZEL, M.D., F.A.C.A.

Foley, Alabama

THE author stresses the importance of adequately controlling the allergic asthma, in order that the tuberculosis may be controlled by collapse therapy.

The type of collapse therapy used will depend much on the absolute prevention of asthmatic attacks. These allergic states must be studied completely and treated by all means, symptomatically, eliminative, and by hypsensitization therapy.

Ten cases are presented which illustrate the difficulty in the diagnosis of asthma in the presence of tuberculosis, the forms of surgical therapy directed toward the control of the tuberculosis, and the dangers of such therapy during asthmatic attacks.

Although the incidence of the two conditions occurring in the same individual is low, the problem that these conditions produce taxes the ingenuity of the physician. The ten cases represent the experience covering the various problems encountered.

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## THE IMPORTANCE OF PREDISPOSING AND CONTRIBUTORY FACTORS IN AN ALLERGIC EVALUATION

NELSON ZIVITZ, M.D., F.A.C.A.

Miami Beach, Florida

IN an allergic evaluation of a patient, skin testing is one part of the search for the exciting agent or allergen. The value of history and conversational study cannot be stressed too much in this evaluation. However, the search for an antigen is an incomplete approach for many patients, and

when this is the total extent of the study, there will be many failures. This is particularly true for foods and drugs but also with pollens and inhalants.

A group of fifty cases are considered, in which eighteen (36 per cent) could not be evaluated or treated properly without attention to predisposing and contributory factors. Furthermore, only the knowledge of these factors will explain the variable reactions to an antigen.

The importance of the home environment in a child, particularly where the parents are highly emotional or where asthma is prevalent, is stressed. The constitution of an individual in general and the skin in particular are exemplified by illustrations of patients. Glandular factors such as premenstrual tension are found to be definite auxiliary factors in the production of symptoms in an allergic individual. Also the relation of hormones on the neurovegetative functions of the body and allergic disease are mentioned.

The altered state of the gastrointestinal tract, by either disease or abnormal physiology from unwise eating habits, bears direct relationship to the allergic tolerance of the individual. One case with a mild pancreatic insufficiency and associated asthma from foods is discussed. It is suggested that reactions to food allergens may be due to variations in the physiology of the gastrointestinal tract, both normal and abnormal.

Both acute and chronic bacterial infections with their precipitating and complicating relationship to allergic manifestations are considered and illustrated by cases. It is pointed out that the same relationship exists with nonspecific irritation from vapors, smoke and odors.

Meteorological and climatic factors with specific reference to the fall of barometric pressure are discussed. It is mentioned that both treated and untreated patients are affected by such factors.

Finally, the psychosomatic factors are considered. It is suggested that psychic trauma be considered an allergen as are light and heat, which also fail to show an antigen-antibody reaction. But, regardless of the designation, psychic trauma is either a predisposing or a contributory factor in many allergic individuals, including those with specific proven sensitivities.

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#### SOCIEDADE BRASILEIRA DE ALERGIA

We are pleased to announce that the Sociedade Brasileira de Alergia has been founded in Rio de Janeiro, Brazil.

The following officers were appointed for one year: President, Dr. U. Fabiano Alves; Vice President, Dr. Paulo Dias da Costa; First Secretary, Dr. J. Greves de Barros; Second Secretary, Dr. Eleuterio Brum Negreiros; Treasurer, Dr. Haroldo Cardoso de Castro; Librarian, Dr. Tamara Rubinstein.

The fiscal Board is composed of the following:

*Permanent Members*—Dr. Rafael Galeno Sidou, Dr. A. Oliveira Lima, and Dr. Olavo Gabriel Diniz.

*Substitute Members*—Dr. Percy Pereira dos Santos and Dr. Antonio Garcia Garbes.

# SPECIFICATIONS RECOMMENDED AS GUIDES IN THE COLLECTION AND PRESERVATION OF POLLENS

Edited by MILTON V. VELDEE, M.D.†  
Bethesda, Maryland

## QUALIFICATIONS OF THE POLLEN COLLECTOR

The collector, or his immediate field supervisor, should have complete courses in college botany and plant taxonomy, or through practical training have acquired equivalent botanical knowledge.

## LABELING THE DISPENSING CONTAINER

The label on the final container should show the following:

The recognized botanical name for the plant involved.

The common name.

The amount of pollen in the dispensing container.

The year when the pollen was collected.

The name and address of the collector.

## PURITY OF THE POLLEN

*Freedom from Other Pollens.*—Contamination with mixed pollens of other species should not exceed 1.0 per cent, or 0.5 per cent with a single pollen, as determined by microscopic count, except that when ragweed pollen is the contaminant the amount of this pollen present shall not exceed 0.1 per cent. There are a few instances involving field-collected pollens when single species pollens cannot be collected to meet these specifications because simultaneously pollinating plants are growing in close proximity to each other. When unavoidable excessive contamination occurs due to this cause, the purchaser of the pollen should be informed.

*Freedom from Flower or Other Parts from the Same Species.*—The amount of extraneous plant material from the same species present in the pollen should not exceed 10 per cent for pollens obtained from those species which do not freely shed their pollens and not more than 5 per cent from free-shedding species.

*Freedom from Non-related Contaminants.*—Pollen should be free of all contaminants not related to the species of plant involved, such as leaves, dirt, and similar substances. An exception is recognized with those plants whose growing habits make contamination with dirt unavoidable; example, creeping pigweed.

## STABILITY OF THE ACTIVE COMPONENT OF THE POLLEN

Freeing the pollen of any extrinsic moisture (due to weather conditions such as humidity, dew, or rain) should commence just as soon as possible after collection. A delay of more than twenty-four hours should not occur when pollens are collected in the field. When plant material is brought to the pollen-collecting shed to await the shedding of the pollen, it is interpreted that evaporation of extrinsic moisture takes care of itself but can be accelerated by proper ventilation and heating of the collecting room.

†Chief, Biologics Control Laboratory, National Institute of Health, Bethesda 14, Maryland. Co-operating in the preparation of these specifications are the following individuals and groups: Representing the allergists: Committee of Therapy, The American Academy of Allergy; Subcommittee on Certification of Allergenic Extracts, American College of Allergists; and Doctors R. A. Cooke and R. F. E. Stier.

Representing the pollen collectors: Wm. B. Hafford, Fred H. Hodgson, Guy Hollister, Cleveland Sharp, and T. R. Stemen.

Representing research: A. Stull, R. P. Wodehouse, and J. J. Wright.

Drying the pollen to free it of intrinsic moisture (moisture naturally occurring in the pollen grain), while not as urgent as removing external moisture (see preceding paragraph), should nevertheless commence with a minimum of delay. With present methods of collecting and drying, this usually can be started within twenty-four hours of collecting the pollen in the field or after completion of shedding in the pollen-harvesting shed. It should never be delayed more than seven days with either method of collection.

Freshly field-collected pollen from which extrinsic moisture has not been removed should neither be packed in a compact layer nor in a closed container. Similarly, freshly collected plant material from which pollen is to be separated upon arrival at the pollen-harvesting shed should neither be packed in compact layers nor in closed containers, if the time required for transportation to the harvesting shed is more than one, two, or three hours, the latter depending on the species of plant. A successful procedure is to place the plant material in thin layers in trays made of wire screening which are then stacked so as to allow the free circulation of air between the layers.

Once drying has been started to remove intrinsic moisture, it should proceed without interruption at not over 65° C. (117° F.) until the moisture content is less than 1.0 per cent; for practical purposes this means until no further loss of weight occurs.

The age of a pollen is indicated by placing the year of collection on the label.

#### TYPE OF CONTAINER

For bulk storage each pollen should be placed immediately after removal from the drier in a clear glass container fitted with a closure capable of excluding atmospheric moisture. Containers of equal quality should be used for the final packaging.

#### CHANGE OF COLOR IN THE DRIED POLLEN

Properly dried pollen when contained in an adequately sealed container does not undergo further color change. An exception exists with some of the Compositae, as for example goldenrod, where there is a progressive color change for one or two months after drying before a permanence of color is reached.

#### CO-OPERATION BETWEEN THE USER AND COLLECTOR OF POLLENS

The user of pollen for the preparation of allergenic extracts should estimate his needs so as to place orders with the collector in advance of the pollen season. This practice will make more certain the receipts of fresh pollen of good quality and in adequate supply. It is suggested that the user require the collector to certify that the stock supplied on order meets the specifications detailed above. A copy of these specifications might be enclosed with the order, with space provided for the collector's certification, and returned with the material. Another method would be for the manufacturing allergist to purchase pollens subject to meeting these specifications on receipt.

#### COMMENTS ON THE SPECIFICATIONS

*Qualifications of the Pollen Collector.*—The collection of pollen, both as it relates to purity and the identification of each collection as to its correct botanical name, demands a certain training in botany. This is best obtained through proper academic training but could conceivably be obtained through practical experience in the field when acquired under competent supervision.

## LABELING THE DISPENSING CONTAINER

The Linnean system of binominal nomenclature should be used in recording the botanical name.

When there is more than one common name, the one best understood by the allergist should be selected.

The amount of pollen in the container is preferably expressed in the metric system.

The age of the pollen should be made known to the allergist. This will continue to be important until the factors which cause loss of antigenic activity are known and can be eliminated.

The collector as used in this section means the primary distributor and does not refer to the particular individual who may have collected the pollen in the field.

*Purity of the Pollen.*—The contamination of a pollen with pollens of other species is objectionable because of the harmful effect it can have on the patient. If the amount of foreign pollen is sufficient, there is a real danger that the resulting extract will cause false reactions and lead to improper treatment of the patient. Pollens vary in their antigenic activity; ragweed being particularly active.

The contamination of a pollen with extraneous plant material from the same species will not lead to deleterious reactions in the patient. However, its presence will reduce the antigenic strength of a finished allergenic extract and therefore is objectionable.

The presence of dirt and other non-pollen substances is a good index of the collector's ability and professional standards. However, there are certain exceptions which must be recognized. The growth habits of some plants and the growing environment in certain instances make it very difficult, if not impossible, to collect the pollen without the admixture of dirt or soil. If this is made known to the producing allergist, corrections can be made at the time of preparing the extract.

*Stability of the Active Component of the Pollen.*—The factors which determine the stability of the allergenic component of a pollen are not fully established. However, it has been shown that storage without adequate drying speeds the rate of denaturation, and more particularly so, if stored at relatively warm temperatures. Extrinsic moisture (due to humidity, dew, or rain) provides favorable conditions for fermentation and souring of the pollen due to the activity of contaminating micro-organisms. Intrinsic moisture (moisture contained in the pollen) is necessary for enzymatic (chemical) activity within the pollen grain. These denaturing activities can be slowed, if not actually arrested, by storage at temperatures well below freezing or by the removal of the moisture to below the critical level for enzyme and micro-organism activity. Storage in an oxygen-free atmosphere would be of benefit. The age of the pollen is probably of secondary significance, provided the moisture is promptly and adequately removed.

At the time of collection the pollen grains are living cells inside of which a certain amount of metabolic (enzymatic) activity is in progress. Intrinsic moisture is involved in this activity and may even be produced by being split off from other compounds during cellular metabolism. This intercellular activity has been termed respiration. The purpose of prompt drying (desiccation) is to arrest permanently this chemical activity.

An ideally treated and packaged pollen would be one which has been dried to less than 1.0 per cent moisture immediately after collection, followed by filling into final glass containers and then hermetically (flame) sealed under vacuum and stored at  $-20^{\circ}\text{C}$ . These are requirements which cannot be obtained easily since pollens are field-grown and therefore must be collected where found. There is always the cost of production to be considered as well. However, having in mind the essentials for an

active pollen extract, it becomes possible to lay down collection and preservation procedures of a practicable character and which should add greatly to insuring the quality of the pollen.

The construction specifications of a very satisfactory drier, and its mode of operation, have been described by Benesford, and Cooke.† A drier of this design, or one of similar design and operating principle, can be constructed at relatively low cost and by a person with ordinary mechanical skill. A drier constructed on this principle must be thermostatically controlled, and preferably time-controlled. With these safeguards, drying may be accomplished without risk of damaging the allergenic activity. The drier is portable and therefore can be carried as field equipment on extended collection trips.

Another method is to dry the pollen in a glass vacuum desiccator of the usual laboratory type. This calls for phosphorous pentoxide ( $P_2O_5$ ) as the desiccant and a source of vacuum, usually a water vacuum pump. When this method is used the operation is carried out at prevailing room temperature. The time interval, beyond the minimum required to bring the moisture content below 1.0 per cent, is not a factor, since no heat is applied. It is important that there should still be active phosphorous pentoxide exposed in the vacuum jar at the end of the drying interval.

Experience will show the observant collector how long it takes to reduce the moisture content to less than 1.0 per cent. As a practical objective this should mean until there is no further loss of weight. In addition, any collector desiring to have his drying method independently checked may do so by submitting no less than a 1 Gm. sample of dried pollen in one of his final dispensing containers to the Biologies Control Laboratory, National Institute of Health, Bethesda 14, Maryland. The large users of pollens, who usually have facilities for making moisture determinations, probably also would be glad to report the moisture content of at least some of their pollen purchases if a report were requested by the collector.

*Type of Container.*—In certain sections of the country the humidity is excessively high. Under such circumstances some collectors and users of pollen have found it advisable to provide their bulk storage containers with a desiccant. It may be placed in a specially constructed lid, or contained in a suitable cloth bag and hung immediately under the lid. Still another method is to store the bulk pollen containers in a compartment provided with a well-fitted weatherstripped door. Space within the compartment is provided for an open tray which is kept filled with a drying agent in active condition.

*Change of Color in the Dried Pollen.*—When pollens are properly dried, the color becomes fixed. Progressive color change after drying is completed is an indication of chemical change within pollen grains. This is likely to mean denaturation of the active principle. It should serve as a warning to the collector that his preserving methods are inadequate.

*Co-operation between the User and Collector of Pollens.*—It is becoming increasingly evident that many factors are at play in determining the allergenic activity of a pollen used in an allergenic extract. The allergist should profit by the well-controlled experiences which the pharmacologist has had with digitalis leaves. In this instance, it has been well established that the geographic area, the character of the soil, the amount of moisture during the growing season, the variety of the plant, the time of harvesting the leaves, and the method employed in their curing largely determine the therapeutic activity of the finished preparation. Without question,

†Benesford, Arthur B., and Cooke, Robert A.: J. Allergy, 15:379-384, 1944.



these same factors are at play with the pollens. The probability of controlling the growing conditions for each pollen is remote. It seems nearly as remote that methods for the accurate biologic assay of a pollen extract can be developed in the immediate future, though the study by Wodehouse† indicates some progress. However, much can be accomplished by a close co-operation and better understanding between the manufacturing allergist and the pollen collector. The acceptance of the above specifications of quality for the pollens will greatly improve the therapeutic activity of the finished extract. The collector should welcome these specifications as a code of operation for the pollen-collecting industry. As a corollary, the manufacturing allergist should be willing to accept the probable small increase in cost involved in collecting and preserving pollens in this way.

†Wodehouse, R. P.: *Ann. Allergy*, 5:203, 1947.

## ALLERGENIC (SKIN-TEST) ACTIVITY OF LOW RAGWEED POLLEN AFTER IRRADIATION OF EXTRACT WITH ULTRAVIOLET LIGHT

(Continued from Page 10)

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## ANNOUNCING A NEW BOOK

"Psychodynamics and the Allergic Patient" is the title of a new book, the first of a series of three, presenting the Panel Discussions given at the annual meeting of the American College of Allergists, to be published in July, 1948.

The historical chapter entitled "Psychosomatic Aspects of Hay Fever Prior to 1900," by Harold A. Abramson, M.D., will appear in the March-April issue of the *ANNALS OF ALLERGY*. Another chapter by Dr. Abramson on "Psychodynamics and the Allergic Patient" will appear in the May-June issue.

Contributors include Harold A. Abramson, M.D., Frank Fremont-Smith, M.D., Franz Alexander, M.D., O. Spurgeon English, M.D., Sandor Rado, M.D., Edward Weiss, M.D., J. A. P. Millet, M.D., Rudolf L. Baer, M.D., Ethan Allan Brown, M.D., Hal M. Davison, M.D., M. Murray Peshkin, M.D., and Homer E. Prince, M.D.

This book will contain about 120 pages, with eight pages devoted to illustrations. Further announcement, including price and other details, will appear in the next issue.

# Editorial

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*The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.*

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## PRESENT STATUS OF CERTIFICATION

According to the resolutions passed at the business meeting of the Fourth Annual Meeting of the American Academy of Allergy in St. Louis, December 15, 1947, and previous action taken by the Board of Regents of the American College of Allergists, a committee appeared before the Advisory Board of Medical Specialties of the American Medical Association on February 7, 1948, in Chicago and presented the following resolutions:

To The Advisory Board of Medical Specialties

Gentlemen:

We, the signers of this petition, representing officially both the American Academy of Allergy and the American College of Allergists and therefore over 1,200 of the physicians of America who at this time are doing clinical allergy, met in Chicago on February 6, 1948, and passed unanimously the following resolution:

WHEREAS, the specialty of allergy since the turn of the century has kept pace with the growth and development of the basic sciences underlying medicine. With the increasing knowledge of immunology and tissue chemistry, the science of allergy now approaches its fiftieth year of development. And

WHEREAS, the clinical specialty of allergy now embraces 1,200 and more physicians who have and are now devoting most of their energies and most of their time to this specialty. And

WHEREAS, the incidents of allergic manifestations among the population at large affects at least 10 per cent of our people. And

WHEREAS, residencies and postgraduate instructional courses in allergy are multiplying yearly throughout the country and are training hundreds of physicians in this specialty. And

WHEREAS, the number of publications in the specialty of allergy is ever increasing. And

WHEREAS, the protection of both the lay and medical public is a responsibility which must be assumed by the allergists.

BE IT RESOLVED, therefore that we, who comprise this Joint Committee representing both the American College of Allergists and the American Academy of Allergy, unanimously agree to support the petition respectfully submitted to your Board by the American Academy of Allergy and the American College of Allergists to establish the American Board of Allergy.

Representing the  
*American Academy of Allergy*

GEORGE PINESS, M.D.

HARVEY BLACK, M.D.

HARRY L. HUBER, M.D.

Representing the  
*American College of Allergists*

HAL M. DAVISON, M.D.

FRED WITTICH, M.D.

M. MURRAY PESHKIN, M.D.

JONATHAN FORMAN, M.D.

## ANTIHISTAMINIC AGENTS IN ALLERGY

For the second time in a year, the New York Academy of Sciences held a conference of considerable interest for allergists on October 3 and 4, 1947, the subject being "Antihistaminic Agents in Allergy." The pharmacology of histamine and that of the antihistaminic agents was considered by an international array of speakers headed by Sir Henry Dale. The printed record, when presented, will offer a comprehensive review of our knowledge in these fields.

One aspect of the problems raised by the study of the effect of the new group of drugs (which came to us from France and which are now undergoing such a comprehensive investigation) merits some comment in this place. Though the pharmacological effects of the antihistaminic drugs are by no means restricted to antihistaminic action, this later one is evidently predominant in the present explanation of the clinical effect. Dr. R. L. Mayer attempted a quite original approach to the question, why these drugs should not be effective in allergic dermatoses of the type of contact dermatitis. Suspecting that in this case additional mechanisms may come into play, he found that hyalinuridase greatly enhances the reaction of dermally sensitized guinea pigs on dermal challenge. He then found that pyribenzamine and its congeners block this effect. These experiments, of course, do not prove that hyalinuridase plays a role in human allergic dermatoses. On the contrary one may argue that the lack of clinical effect of antihistaminic drugs speaks against such an effect. But whatever their significance for the action of the antihistaminic drugs, Mayer's data give a stimulating example of experimental analysis. And they will get the dermatologist to work on a hitherto unsuspected aspect of dermal pathology.

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## EFFECT OF RUTIN ON ANAPHYLACTIC AND HISTAMINE SHOCK

According to a recent article, rutin protects against anaphylactic shock. Raiman, Later and Necheles,<sup>†</sup> working at the Michael Reese hospital in Chicago, report that guinea pigs receiving 2 mgs. of rutin intraperitoneally thirty to forty-five minutes before anaphylactic shock was attempted, not only received protection against anaphylactic shock but also manifested no symptoms. These experiments were performed on three series of animals under different conditions. Of twenty-one guinea pigs, nine animals were given 1 mg. of rutin intravenously thirty to forty minutes before receiving the minimal lethal dose of histamine. All of the animals in this series died, exhibiting the characteristic symptoms of histamine shock. These results demonstrate that rutin protects guinea pigs against the fatal effects of anaphylactic shock but not against those of histamine shock.

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<sup>†</sup>Effect of rutin on anaphylactic and histamine shock. R. J. Raiman, E. R. Later, and H. Necheles. *Science*, October 17, 1947.

The authors point out that if it is assumed that rutin protects against anaphylactic shock by virtue of its "tightening effect" on the capillary endothelium, then histamine may be excluded as the lethal factor of anaphylactic shock. In the guinea pigs injected thirty to forty minutes before anaphylactic shock was attempted, no bronchiolar spasm was apparent. Their lungs were found to be normal. On the other hand, histamine injected produced the syndrome of protein anaphylactic shock with bronchiolar spasm and changes in the lungs. According to the authors, the possibility exists, that the protective effect of rutin may be that it prevents the liberation of endogenous histamine by unknown factors other than those which increase capillary permeability. It may be recalled that Hiramatsu found that guinea pigs were protected against anaphylactic shock by large doses of hesperidin.

Irrespective of the way in which rutin acts, it is apparent that the simple histamine theory of allergy requires extensive modification since, with increasing knowledge, its foundation becomes increasingly less certain.

### PHYSIOLOGY OF THE LUNGS AND THE ASTHMATIC STATE

Although allergists have been primarily interested in immunological mechanisms and more recently in those connected with psychodynamics, it should not be forgotten that the physiology of the lungs is of prime importance in elucidating the many phenomena connected with the asthmatic state.

A recent paper by Mack, Grossman and Katz (*Am. J. Physiology*, 150:654, 1947) points out how pulmonary congestion may operate to bring about dyspnea. Mechanically, one of the important factors is the change in the distensibility of the lung. When the pulmonary vessels become engorged, their rigidity increases. Thus, they act like a hose turgid with water under pressure. It is readily accepted that this may be a contributing factor in the increased respiratory effort observed in congestive heart failure. But this diminished distensibility also may contribute to a diminution in vital capacity and even to the formation of intra-pleural transudates.

Mack, Grossman and Katz demonstrated directly the effect of congestion of the pulmonary vessels on lung distensibility with fresh lung preparations obtained from dogs and in the intact animal. They found that the injection of blood into the pulmonary circulation causes a decrease in the distensibility of the lung proportional to the amount of blood introduced. When almost all of the blood injected was siphoned off, the distensibility curve was restored. This demonstrated clearly that the effect was due to intravascular blood which could be siphoned off, and not to an intra-alveolar transudate similar to that found in pulmonary edema.

*(Continued on Page 93)*

# Progress in Allergy

## BRONCHIAL ASTHMA (IV)

### Critical Review of Literature

LEON UNGER, M.D., F.A.C.A., and BENJAMIN F. GORDON, M.D., F.A.C.A. (Assoc)

Chicago, Illinois

In the eighteen-month period from January 1, 1946, to June 30, 1947, there have been published new books and a large number of articles which deal with various kinds of asthma and its closely related clinical conditions. These will now be reviewed in much the same way as in the previous reviews on this subject which covered the literature of 1943,<sup>349</sup> 1944,<sup>350</sup> and 1945.<sup>351</sup>

Some of this literature is not new, but much is devoted to the increased use of penicillin and the so-called antihistaminic drugs. The authors have faithfully tried to cover all the articles on the subject from all over the world. We realize that we have omitted some and beg the authors' indulgence. Some journals cannot be obtained, but most of the omitted articles are written in languages foreign to us and we have not been able to obtain satisfactory translations. We therefore suggest to authors who write in Spanish, French, German, Russian, Portuguese, Scandinavian, et cetera, that they end their articles with a comprehensive summary in English. This will insure proper credit in the future. Incidentally, those who write in English might reciprocate. We would also be pleased to receive reprints, with translations or abstracts, of foreign articles.

#### NEW BOOKS

Arranged in alphabetical order, twelve new books have been written either on asthma or on various phases of allergy, including asthma.

Gianfranco Capuani<sup>50</sup> has written an 829-page book on *Allergia e Malattie Allergiche*. The book was published in Torino, Italy. It is an excellent volume, with a good discussion of fundamental and clinical subjects, well-illustrated, and with an extensive bibliography.

Cooke's *Principles of Allergy in Theory and Practice* has attracted much favorable comment and some opposition. Dr. Cooke wrote most of the book, but thirteen associates contributed some chapters. The fundamental and theoretical aspects of allergy are excellently portrayed, though some readers do not believe that the role of infection is as important as stated. Skin testing is practically only by the intradermal method, a serious error because of possible constitutional reactions. The chapters on bronchial asthma are good but not adequate as regards details of treatment.

*It's An Allergy*, by Crandall,<sup>52</sup> is a comprehensive book on allergy written for the patient, with a chapter on asthma. It gives good advice to the patient, and its large bibliography may lead some patients to learn more about their allergies. This may or may not be a blessing, depending on the patient. There are interesting case reports.

*The Treatment of Bronchial Asthma*, by Derbes, Engelhardt, and their associates,<sup>53</sup> is a good book. The first eight chapters are devoted to basic material, including good chapters on anatomy, physiology and pathology of the respiratory tract. In the next fifteen chapters there is a discussion of intrinsic and extrinsic factors in bronchial asthma. Worthy of special mention are the chapters on the role of foods by Wittich, differential diagnosis by Soderman, nonallergic treatment by La Due, and statistical survey by Dublin and Marks. Because of its size, some details of treatment are necessarily omitted. A larger revision by these authors, with a more extensive bibliography, would be welcome.

Feinberg's *Allergy in Practice*, second edition,<sup>109</sup> contains much new information, especially as regards mold allergy, vascular allergy, and tropical eosinophilia. There is an informative chapter on histamine by Dr. Carl Dragstedt, and an extensive and excellent chapter on pollens by Durham. Some of the newer information on asthma is also listed, as well as information on histamine antagonists.

*Allergia en la Practica Clinica*, by Fuentes, Recarte, and Graña,<sup>121</sup> from Montevideo, Uruguay, is a large and pretentious book on all aspects of allergy. In addition

Review covers period from January 1, 1946, to June 30, 1947

tion, there are chapters on hydatid diseases, eosinophilia, and lymphogranuloma inguinale, and much on tuberculin allergy. The book is well written and should be translated into English and other languages. Like most contributions from South America, it emphasizes the predominant role of foods. Inhalant allergy seems much less important than in North America.

Leslie Gay's *Diagnosis and Treatment of Bronchial Asthma*<sup>148</sup> gives the experiences in this field of one of the pioneers in the field of allergy. There are excellent discussions of the physiology, pathology and psychosomatic aspects of asthma, with case reports. The book is rather small, and because of excessive space given to particular subjects, the author has been forced to curtail discussion of many more important points relative to bronchial asthma. The reader is urged to consult the book reviews.<sup>137</sup>

*Diseases of the Chest With Emphasis on X-Ray Diagnosis*,<sup>295</sup> by Rubin and Rubin, is an outstanding work. The illustrations, with twenty-four plates in color, are excellent. Both pulmonary tuberculosis and nontuberculous diseases of the chest, including asthma, are discussed. There are excellent chapters on surgical treatment of empyema, lung abscess, cancer, tuberculosis, and benign tumors. Two chapters are devoted to obstruction of the bronchi.

*What You Don't Know May Hurt You*<sup>297</sup> is a small volume by Rudolph and Rose. By case reports and simple, humorous language the laity is informed about some phases of allergy. Some reports are rather sensational, but this aspect is probably necessary to interest the public.

*Asma Alergia (Asthma Allergy)*, by Ruiz-Moreno,<sup>298</sup> contains 186 pages; the first 139 are given to asthma, the rest to allergy in general. The book is small but contains much information, some old, some new. Chapter X is interesting because it deals with social problems of asthma, including eugenesis, legislation, asthma in military service, prophylaxis (industrial), and professional re-education.

Sterling has written another small book entitled *Clinical Allergy*.<sup>327</sup> Case reports are interesting but important details are lacking.

Last, but by no means least, is that tremendous book entitled *Allergy*, second edition, by Urbach and Gottlieb.<sup>352</sup> This edition is even better than the first. There are over 3,300 references, a thousand more than in the previous edition. The book is extremely valuable because it covers the entire field of allergy. A great deal of new material has been added, including sections on psychosomatic aspects and drug allergy. A large part of the book is devoted to dermatologic conditions. The only part of the book open to American criticism is the continued thinking and terminology of the European; these things never have and probably never will be accepted by those of us trained in the United States.

These reviewers earnestly advise future authors of books to write very large books if they wish to cover the entire field of allergy. If an author concentrates on a limited subject, such as bronchial asthma, hay fever or migraine, his work should still be large enough so that the reader can obtain sufficient information to help him in his particular cases. A good bibliography is absolutely essential, and it should be broad minded so that both sides of the question can be represented.

#### MILITARY REPORTS

The number of articles from the armed services is naturally decreasing. The war is over, but inasmuch as some of our forces are still scattered over the world, we must continue our interest in the military aspects of asthma and other allergic diseases. Asthma is the main allergic cause of disability and discharge.

A wonderfully satisfactory report concerns the incidence of tetanus in the United States Army in World War II. Long and Sartwell<sup>223</sup> report that tetanus toxoid was given to all except a few who were very sensitive to it. After immunity was established, booster or stimulating doses were given at the end of one year and for injuries. Adequate response to booster doses was observed for a period of at least three years after basic immunization and for two years after the routine stimulating dose. The protection probably lasts even longer.

Throughout the entire war period there were only twelve cases of tetanus in the entire army, including four from injuries sustained prior to entry into active duty. Only six of these had received basic immunization, and only four had the emergency stimulating dose. Death occurred in five of these twelve patients; of these, two had received full prophylactic immunization plus emergency booster doses after injury.

Compared with the incidence of tetanus in World War I and in the intervening years with (1) civilian mortality, (2) incidence in enemy forces, and (3) incidence in civilians injured during military operations, it is gratifying to note that the army's preventive treatment was highly effective. Reactions from tetanus toxoid were

infrequent, and when certain peptone components were removed, reactions dropped to a frequency of less than 2 per 100,000 injections.

Two reports come from the U. S. Navy. Blue,<sup>35</sup> in an article on allergy in the Pacific, concludes: (1) There is an apparent increase in allergic conditions in the armed forces. (2) Psychogenic factors are of greater importance than in civilian life (this point is emphasized in almost all reports from the services). (3) The allergic conditions themselves are about the same in the Pacific area and in Continental U.S.A. (4) Of 500 patients, 293 (58.6 per cent) had bronchial asthma, and fifty-six (11.2 per cent) had hay fever. (5) The average duration was eight years. (6) As regards asthma, 17.4 per cent had their first symptoms in this area, and in 86.6 per cent symptoms were aggravated while in the Pacific. (7) In 61.3 per cent of the asthmatics, good results were obtained, but, because of military necessities, only 15.7 per cent were returned to duty; the rest were sent home as unfit for combat duty.

Smith<sup>318</sup> concludes that bronchial asthma cannot be successfully treated in a military environment where many factors are beyond the control of the physician. In a study of 100 cases of chronic asthma, he found that it caused disability over longer periods of time than most illnesses (average time on sick list was 114.5 days per patient). Seventy-eight per cent of these asthmatics had a positive pre-enlistment history of asthma. Skin tests were positive in 70 per cent, and 41 per cent cleared under treatment, yet as with Blue, only 18 per cent were returned to duty. These figures bear out the wisdom of the navy in not knowingly accepting men with pre-existing asthma.

There are five reports from the army, and the similarity in these and in those analyzed in previous years<sup>349-351</sup> is striking. Fishman<sup>115</sup> studied 100 asthmatics returned from the European Theater of Operations (North Africa, Italy and France). All were evacuated because their asthma prevented them from performing even limited duties in the service. Fishman divided them into three groups:

- (A)—(Fifty-six cases) No history of previous asthma before overseas arrival.
- (B)—(Fourteen cases) An initial attack in civilian life followed by an asymptomatic period which was terminated by arrival overseas.
- (C)—(Thirty cases) Recurrent asthma in civilian life which became incapacitating overseas.

No symptoms were present in seventy-eight when they reached the United States, and these needed no further treatment. Emotional factors were especially severe in eighteen cases and were much more important in Group A. Groups B and C were composed of individuals who fully satisfy the diagnostic criteria for allergic disease (high percentage positive skin tests, previous attacks of asthma, higher percentage positive family history). Asthmatics constituted 1 to 3 per cent of the total number evacuated to the United States—this despite all efforts to keep asthmatics out of the army.

Winkenwerder<sup>373</sup> agrees that 1 to 2 per cent of admissions to his hospital in the Southwest Pacific Area were for asthma. He studied 209 cases, most of whom gave a positive personal or family history for allergy and/or gave positive skin tests. Of 102 patients whose attacks began in the service, in 64 per cent, the first episode occurred in the tropics, in 16 per cent in Australia, and in 20 per cent in the United States. In the tropics, hay fever was associated with the asthma in about 50 per cent of cases. Symptoms were usually perennial, and many developed asthma within two weeks after arrival in the tropics, the majority within three months.

The chief allergens: grass and algeroba tree pollens, mold spores, and tropical dust, which has about twenty times the protein nitrogen content as compared with dust in the United States. Contributory factors included excessive humidity, wide variations in daily temperature, strong aroma of molds, and the rigors of military life. The average disability period per man was about two months, and 82 per cent had to be returned to the states.

Rosen<sup>291</sup> studied 100 asthmatics admitted to an army hospital from June, 1944, to March, 1945, with an average stay of one month. Mild symptoms occurred in nineteen, moderate in seventy-four, severe in seven. The first group was put on limited duty; the rest were discharged from the service.

One patient had a coincident asthmatic bronchitis; all the rest had uncomplicated bronchial asthma. There were no deaths. Asthma was perennial in eighty-seven, seasonal in thirteen. Associated nasal symptoms were present in fifty-five cases, thirty of which were perennial and twenty-five seasonal. One interesting point was

that the first attack of asthma in seven of ten ragweed asthmatics occurred at the camp; these seven came from areas with less previous exposure to ragweed to this hospital which was located in a part of Indiana noted for the highest ragweed pollen counts.

In another article, Rosen<sup>293</sup> compared asthma in fifty patients returned from the tropics with fifty who had not been outside of the United States. In the first group, 40 per cent had their first attack of asthma while in the tropics; in the U. S. group, only 14 per cent had their first attack after induction. There was no great difference in blood eosinophilia (5 per cent or over) between the two groups (42 per cent and 32 per cent), and x-rays of the chest were normal in 84 and 82 per cent, respectively. On skin testing, 42 per cent of the "tropical" group reacted to timothy, with only 26 per cent in the U. S. group; on the other hand, reactions to feathers were six per cent and 24 per cent, and the U. S. group also showed more positive reactions to food extracts.

Zoss<sup>350</sup> and his associates studied the nasal, sinus and bronchoscopic findings in 250 soldiers who had perennial asthma and were stationed in Georgia. Of these, 81.4 per cent had been overseas. More developed asthma for the first time while in the Southwest Pacific than in either the European or China-Burma-India sectors. Of the entire group, 43.2 per cent had asthma for less than five years.

Examination revealed that 50 per cent of the patients had chronic suppurative sinusitis. Bronchoscopic examinations were done in all cases and revealed abnormalities in 89.6 per cent. The authors divided these: (1) chronic suppurative bronchitis in 49.2 per cent, (2) chronic nonsuppurative bronchitis in 38.8 per cent, and (3) allergic bronchitis in 1.6 per cent. In the whole group, chronic respiratory tract infection was found in 73.2 per cent.

[These high percentages as regards infection are extremely surprising. It is hardly likely that military service can be of that much importance in this regard. The authors admit that cytological and bacterial investigations of the bronchial secretions were not done in all cases, due to circumstances beyond their control. Are we to rely on observation of the nasal and bronchial mucosa alone to say whether infection or allergy or neither exists? The authors state that "the finding of mucopus was considered reliable evidence of bacterial infections." This is not true, as shown by Hansel and others, who have pointed out over and over again that a predominance of polymorphonuclear cells in the nasal secretion indicates infection, whereas eosinophilia occurs in allergic rhinitis. Similar findings occur in sputa. If infection had really been so frequent in these young asthmatics, they should have had elevation of temperature, leukocytosis, and an increased sedimentation rate, and they should have been helped by chemotherapy (authors report little benefit).]

#### TROPICAL EOSINOPHILIA, LOEFFLER'S SYNDROME, PERIARTERITIS NODOSA

Confusion still exists in differentiating these three conditions. High blood eosinophilia remains outstanding. Are they related? The reader is urged to study again the discussions in the three previous reviews.<sup>349-351</sup>

*Tropical eosinophilia* continues to be interesting. As stated previously,<sup>351</sup> it "occurs chiefly, but not exclusively, in the tropics, especially in India. The chief symptoms are an insidious onset, with malaise, low-grade fever, headache, and unproductive cough; wheezing and dyspnea are often associated. Leukocytosis (up to 60,000) and marked blood eosinophilia (up to 89 per cent) are striking features. Chest x-ray films usually show fine mottling in both lungs. One to six intravenous injections of neoarsphenamine or other arsenical product cause prompt relief with disappearance of leukocytosis, eosinophilia, and the so-called 'asthma.' No causative organisms have been found."

New reports emphasize that the disease is not confined to India. Wilson<sup>371</sup> did differential white counts in a consecutive series of thirty-four patients attending the native civil hospital in Dar-es-Salaam, Tanganyika, East Africa. These persons had symptoms of recurring bronchitis or asthma. In six, the eosinophilia ranged from 40 to 78 per cent. This group and a seventh patient who had an unexplained eosinophilia had tropical eosinophilia. Six were treated successfully with arsenic; the seventh recovered spontaneously. The characteristic picture consisted of cough, wheezing, and low-grade fever, separated by periods characterized by morning spasmodic cough. Wilson does not believe this condition is the same as Loeffler's syndrome.

Blue<sup>35</sup> noted that four of his patients in the Southwest Pacific had tropical eosinophilia. In all cases, epinephrine relieved attacks of "asthma," but complete relief and reduction in blood eosinophilia followed arsenical therapy. One patient had been in



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Shanghai, and all had been in New Zealand, Samoa, and the Wallis Islands. Despite extensive search, no parasites were found.

Irwin<sup>179</sup> reviews previous findings and adds two new cases in soldiers who had returned after duty in the Southwest Pacific. Their symptoms and laboratory findings were similar to those reported by others, and careful clinical and laboratory studies also failed to establish a cause. Both patients recovered after arsenical therapy, and Irwin believes that intravenous injections gave much better results than did oral (carbasone) treatment.

Telles,<sup>340</sup> in Brazil, found in a child aged nineteen months the clinical, roentgenologic and hematologic aspects of tropical eosinophilia. Fever, failure to gain weight, cough with nocturnal paroxysms, and enlarged lymph nodes were present. Although eggs of *Necator* and *Trichiuris* were found in the feces, all symptoms and findings remained after treatment of the verminosis, but improvement followed intramuscular injections of arsenic. Another case is that of a European male who spent twelve years in Nigeria and returned to England. Six months later, according to Hunter,<sup>174</sup> nocturnal asthma began. He showed 12,400 white cells, with 59 per cent eosinophiles; his chest x-ray film was negative. Later, his count jumped to 36,200 white blood cells with 74 per cent eosinophiles. Three injections of novarsenobillon at weekly intervals led to rapid improvement in symptoms and to a normal blood count.

- Another four articles come from India, the chief site of this condition. Jhatakia,<sup>188</sup> in an excellent paper, points out the frequency in India, especially in Bombay. He has seen 200 cases in the past eighteen months. The etiology remains obscure (allergic? parasitic? virus? spirochetal?). Many of his patients lived in grain centers or worked in grain shops. White blood cells varied from 10,000 to 90,000, and the percentage of eosinophiles from 15 to 92. The x-ray findings may be similar to that in tuberculosis, and many show diffuse mottling. All findings clear when improvement occurs. Nair<sup>249</sup> is cautious. He says that the diagnosis of tropical eosinophilia can only be made with reservations, as pulmonary symptoms and blood eosinophilia can be due to various other known or unknown causes. The value of arsenic therapy as a "diagnostic test" is great, but not absolute; such therapy is also effective in other conditions. If filarial infection can cause eosinophilia and respiratory symptoms simulating tropical eosinophilia, as it did in one of Nair's patients who lived where filariae are prevalent, confusion in diagnosis can occur. Chauda<sup>64</sup> reports that a patient was markedly improved after six injections, 3 c.c. doses each, of acetylarsan (M & B).

Hall<sup>151</sup> favors the theory of infestation by mites as cause of this condition, and likes the term "pulmonary acarasis." One of his patients had never visited the tropics. Both had worked for many hours in hot, damp, and dusty store rooms. Hall points out that Engel (1935) described several cases of "privet asthma" with high blood eosinophilia long before Weingarten's articles. Carter and D'Abbrera<sup>60</sup> also favor the mite theory. Various species of mites were found in the lungs or urine of twenty-five Ceylonese patients who had respiratory symptoms for three weeks to seven years, with prompt relief after arsenical therapy. The types of mites found in the sputum were essentially those commonly associated with store products, dust and debris; these mites are inhaled and the authors believe that they breed in the lungs or bronchi. These findings are similar to those reported in 1945 by Soysa and Jayawardena,<sup>322</sup> also in Ceylonese soldiers.

From the Netherlands West Indies, Van der Sar<sup>337</sup> also favors the mite theory. "Asthmatic bronchitis" was the chief complaint in four of eight patients; the other four had persistent cough without wheezing. Mites were found in the sputa of all, but repeated stool examinations for ova and parasites, and nightly blood examinations for microfilariae proved negative. Those who wheezed had from 58 to 80 per cent blood eosinophilia; of the four who did not wheeze, three had 14 to 18 per cent, and the other only 1 per cent. In five cases, x-ray showed pulmonary infiltrations characteristic of the "eosinophilic lung;" in two cases it suggested Loeffler's syndrome. In all cases treatment with Mafarside or Carbarson was successful, with no recurrences. Lavier's<sup>320</sup> paper is more or less a review, with a differential diagnosis from Loeffler's syndrome.

Probably the first autopsy report in tropical eosinophilia has just been reported by Viswanathan from Calcutta.<sup>323</sup> A twenty-eight-year-old man died of arsenical encephalopathy after the second injection of novarsenobillon. Microscopic sections suggested an infective process rather than an anaphylactic reaction. The lesions are peribronchial, not perivascular. These findings suggest that infection in tropical eosinophilia is probably by inhalation. [This supports the "mite" theory.] The in-

fecting agent is thought to get into the peribronchial tissue and start inflammation which involves the interstitial tissue mainly, the alveoli partially. Discrete scattered areas of cellular infiltration, monocyte and eosinophilic, are produced. When the process becomes chronic, nodules containing giant cells and monocytes are formed; these areas are probably the cause of the disseminated mottled shadows seen in the x-ray films in tropical eosinophilia.

*Loeffler's syndrome* is also intriguing. Herbut and Kinser<sup>161</sup> gave horse serum intratracheally to sensitized rabbits. In a few minutes, cough developed, with sneezing, inspiratory dyspnea, and a rapid recovery; a few râles were noted in all animals. With each instillation of horse serum, respiratory symptoms were increased, and finally, anaphylactic death occurred in one rabbit. Slight leukocytosis was present. The x-ray showed transitory (but not migratory) pulmonary infiltrations which cleared in seven to thirteen days. The lung parenchyma revealed congestion, edema, eosinophilic pneumonia, and emphysema. The trachea and bronchi were also congested, edematous and infiltrated by eosinophiles. This picture is, therefore, like that reported by Schlect<sup>162</sup> in guinea pigs.

There are several reports in the human. Eichwald and Singletary<sup>164</sup> discuss a woman who had had a pelvic operation. Later she developed slight fever and vague symptoms and had 21 to 29 per cent blood eosinophilia. Her roentgen findings varied from a linear shadow interpreted as thickened pleura to rather an extensive irregular bilateral mottling which changed frequently. There was no response to antibiotics and no parasites were found. Alpher's first patient,<sup>12</sup> a chronic asthmatic who was sensitive to inhalants, had two and perhaps three attacks of Loeffler's syndrome; his other patient had ragweed hay fever when the syndrome developed. Alpher therefore suggests that the etiology of Loeffler's syndrome be divided into intrinsic (infectious) and extrinsic (pollens, drugs, et cetera).

A two-year-old boy, with a past history of "asthmatic bronchitis" and eczema, developed a septic type of fever for several months, together with severe anemia, leukocytosis, and persistent eosinophilia up to 84 per cent. X-ray showed pulmonary infiltration. The liver was large, and biopsy revealed focal necrosis. The child vomited an adult ascaris, and recovery was rapid though eosinophilia up to 34 per cent persisted.<sup>161</sup>

Sethna's patient,<sup>161</sup> from India, was wrongly diagnosed as a victim of pulmonary tuberculosis. Instead, he had a history of amebiasis, hookworm and ascariasis; he was allergic to the rays of the sun, had blood eosinophilia, and migratory and transitory consolidations on x-ray, and negative findings as regards tuberculosis. Sethna discusses Loeffler's syndrome in detail. Vaccarezza and Pavlovsky<sup>163</sup> report this syndrome in an allergic patient who developed urticaria, dyspnea and cyanosis after injections of gold salts. X-ray showed disseminated lesions, first of the nodular and then of the micronodular type.

Martinez<sup>125</sup> discusses all phases of the syndrome and has eight x-ray illustrations showing patchy infiltrations with clearing and recurrences. Wright and his associates<sup>177</sup> found that twenty-four (9 per cent) of 268 consecutive asthmatic patients admitted to the hospital at Camp Blanding, Florida, had x-ray evidence of pulmonary consolidation. Ten of these were diagnosed as of virus etiology because of fever and systemic symptoms. The remaining fourteen (5.3 per cent) were thought to have allergic consolidation, although they did not conform strictly to Loeffler's criteria, i.e., they did not have migratory infiltration and high blood eosinophilia. On the other hand, they were not typical of virus pneumonia because of absence of fever and systemic symptoms. They point out that mild cases of atypical virus pneumonia occurring in asthmatics can easily be confused with allergic consolidation. The same authors,<sup>178</sup> in a study of fifty-two cases of creeping eruption (cutaneous helminthiasis), found that twenty-six developed pulmonary lesions of the Loeffler type, with the usual paucity of systemic symptoms, but with blood eosinophilia. In 75.5 per cent of the cases, skin tests were positive for ascaris and trichina antigens, but examinations of the stools were negative for nematodes and ova, and no larvae were found in sputa. The pulmonary lesions in these twenty-six patients might be due to dead larvae in the lungs or to sensitization of the host to exotoxins elaborated by subepidermal larvae.

The subject of Loeffler's syndrome has evoked editorial comment,<sup>70</sup> with discussion of the role of allergy from extrinsic materials and as part of various clinical conditions. Autopsy reports have been very few to date and much remains to be learned.

*Periarteritis nodosa* has also attracted attention, both in the human being and in the experimental animal. Diaz-Rivera and Miller<sup>162</sup> found no etiologic agents in

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seven patients who came to postmortem examination. Allergy was suggested as a factor in three, because of eosinophilia and migraine in one case and because of a rash in two others. The duration of symptoms was short and the onset acute, and the symptoms were so varied as to lead to frequent mistakes in diagnosis. In Goldsmith's case<sup>143</sup> the diagnosis was based on finding aneurismal dilatation of the inferior temporal artery on examination of the fundus in a patient who had received prolonged sulfonamide therapy. This is one of five cases in the literature in which fundus examination led to the correct diagnosis.

Higgins<sup>165</sup> presents six clinical cases with postmortem findings in one. The symptoms varied a great deal, as usual, depending on the organs involved and on the stage of the disease. Eosinophilia, if present, is of great aid as regards diagnosis, otherwise laboratory findings are not helpful. Periarthritis nodosa should be suspected in all patients with obscure and generalized symptoms.

Logue and Mullins<sup>221</sup> review the literature (177 cases): eosinophilia was found in 33 per cent, a history of allergy in 21 per cent. They believe that the etiology is diverse, perhaps due to sensitization to serum, drugs and infections. They add eleven cases, ages fifteen to sixty-five, with duration of illness from two and one half to twelve months. One patient recovered and was still well two years later. Hypertension was present in all at some stage of the disease, but there was no personal history of allergy, and none had received sulfonamides. Leukocytosis occurred in all, but eosinophilia in only five. An eleven-year-old boy developed periarthritis nodosa after the third week of scarlet fever, according to Peale and his associates<sup>259</sup>. There was a history of food allergy. Death was due to intracerebral hemorrhage and renal failure, and autopsy revealed vascular lesions in all organs.

Pettit<sup>262</sup> found very extensive pathologic changes at autopsy in a sixty-three-year-old female who was sick for eight years. She had fever, leukocytosis, albuminuria, hypertension, edema, and many other symptoms. The white blood count ranged from 7,300 to 62,000 with many monocytes; eosinophiles were never more than 3 per cent. Moschowitz<sup>248</sup> states that the clinical aspects of this condition result from three large clinical backgrounds, i.e., rheumatic fever, glomerulonephritis and malignant hypertension, plus the consequences of the widespread lesions which affect the circulation and the function of many organs. It can occur at any age, occasionally in infancy.

Miller and Daley<sup>238</sup> review the literature and add nine cases. Males predominate three to one; the disease is most common in the third decade, the average duration is six to twelve months; recovery may occur with little or no residual disability; any organ can be affected, but especially the kidneys, blood eosinophilia occurs in less than 20 per cent. The experimental evidence points to a reaction of hypersensitivity. The authors suggest that Loeffler's syndrome, Libman-Sacks disease, and lupus erythematosus represent localized forms of acute arteritis and are analogous in nature and etiology to periarthritis nodosa.

Bergstrand<sup>25</sup> discusses four patients, aged seventeen to forty-three, who died after illness ranging from six weeks to three years. All had manifestations of asthma, blood eosinophilia, severe diarrhea, hemoptysis and pleurisy. One also had painful joints. Autopsies revealed lesions typical of periarthritis nodosa in many organs, and also evidence of polyarthritis rheumatica. The lung changes were very similar to those described by von Mayenberg as characteristic of acute transient lung infiltration. Changes closely resembling those found in rheumatic pneumonia ("Fruhinfiltrat" and rheumatic granulomas) were found. Bergstrand also believes the etiology can be extrinsic or intrinsic.

Thus we see that confusion still exists as regards tropical eosinophilia, Loeffler's syndrome and periarthritis nodosa. Each has its peculiarities but there is much in common; the differential diagnosis between them is not easy.

### ETIOLOGY OF ASTHMA

Inheritance in respiratory allergy has been studied by Stiles and Johnston<sup>328</sup>. In a family of five generations with 232 individuals, respiratory allergy occurred in 22.4 per cent in contrast with approximately 7 per cent in the general population. Perfect Mendelian ratios are not likely to be obtained in such a study, due to the complexity of both hereditary and environmental factors. The specific sensitivity is not inherited, merely the capacity to become allergic. Symptoms are influenced by the atopic climate, degree of inheritance, age, sex, and other factors. Respiratory allergy may be of an irregular dominant character. The gene exhibits low penetrance with variable expressivity.

Ciprat<sup>17</sup> from Brazil, found that asthma and spasmodic rhinitis are hereditary in 18.02 per cent with the rhinitis occurring in only 5.48 per cent. There was a family

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history of tuberculosis in 15.1 per cent, and almost every patient was sensitive to more than one substance.

Two reports come from Palestine. Melamed,<sup>236</sup> in a study of children under seven in the Sick Fund of the southeastern district of Tel-Aviv, found twenty-three cases of bronchial asthma and forty-six cases of asthmatic bronchitis in 1,400 children seen during the first year of the study. In the second year, 1,600 children under seven were seen, with thirty-seven cases of bronchial asthma and sixty-eight of asthmatic bronchitis. Asthma began in the first year of life in 5 to 6.5 per cent of cases, but most cases began between four and six. The majority of attacks were in September through November, the least in August. Statistics are not entirely accurate as in all surveys of this kind. Confusion exists because, as Glaser says, some authorities say that asthmatic bronchitis is a form of bronchial asthma.

Lass<sup>208</sup> states that allergic diseases are relatively more frequent in Palestine, probably because two-thirds of the population are immigrants who are exposed to new climatic conditions and new plants and substances. The actual incidence is unknown as many sufferers do not report for treatment. One-third of the population is cared for by a Sick Fund, and asthma in 1944 occurred in 0.98 per cent of those who reported sick (in England asthma occurs in about 0.6 per cent and in the United States in about 0.5 per cent). There are marked variations of surface contour, climate, soil and flora in Palestine, with 2,400 different varieties of flora. No season is free from blossoming. *There is a variation in cities, with asthma (for six years prior to 1944) occurring in 0.42 per cent in Samaria to 2.11 per cent in Jerusalem.* The incidence is lowest in rural districts and increases toward the shore line. The highest incidence of asthma occurred in children from one to thirteen (44.9 per cent). The incidence of allergic diseases is high and poses a serious social problem, especially among the poor in Tel-Aviv. The Sick Fund there has a large allergy clinic.

Pediatric allergy is stressed by Chobot,<sup>65</sup> but we dissent from his views that food sensitivity plus bacterial infection comprise the entire cause of asthma in the first few years of life. He states that when food sensitivity causes the asthma this sensitivity disappears spontaneously and the child has a free period until inhalant substances suddenly assume a major role. Bacterial infection is very important, and he therefore urges clean removal of tonsils and adenoids and the use of autogenous vaccines. [Our experience differs in that we rarely see that free interval, nor do we find foods the predominant cause of asthma at any age. Inhalants, we find, are the most important cause of asthma in infants, children and young adults. We do not deny the importance of bacterial infection, but removal of tonsils and adenoids, in our experience, has rarely led to cessation of attacks].

### HOUSE DUST

The importance of the *house dust antigen* is becoming more widely recognized, especially by those who test with potent extracts by both the scratch and intradermal methods. A strong positive scratch test to a good extract such as that made by Endo Products is almost always good evidence for clinical sensitivity. Those who still rely on the old-fashioned dust extracts which must be tested in strong dilutions and by the intradermal route are urged to do scratch tests with this extract. They will open their eyes in amazement and will not be so insistent on the importance of food allergy and infection, especially in children.

Efron<sup>103</sup> describes the usefulness of his purified dust extract, made according to the Boatner process and sold by Endo Products, Inc. Scratch tests are accurate in 90 per cent of the cases in which positive reactions occur; and in about 75 per cent of patients with asthma and/or allergic rhinitis, the scratch test with Endo dust is positive. Intracutaneous tests can be done but are unnecessary in most cases. This dust extract is dissolved in glycerol-saline solution (50 per cent glycerin by volume), and dilutions are made with 0.4 per cent phenol in normal saline.

Oliveira Lima,<sup>252</sup> from Brazil, believes that house dust contains a specific antigen, not present in other indoor inhalants. In eleven atopic individuals (three with perennial rhinitis, two with bronchial asthma and six with both), six gave positive reactions only to house dust; the other five were also sensitive to foods but not to other inhalants. All tests were done intracutaneously, the dust in a 1:100 buffered saline solution. Passive transfer was positive for this dust extract in all eleven patients and entirely negative with the thirty-four inhalant extracts with which tests were also made.

Rockwell, Thomas, and Wittich<sup>290</sup> are to be commended for their report on standardization of house dust extracts. They headed a committee for the American College of Allergists, and for over a year they prepared and tested various dust extracts. Other members of the College collaborated in this work; members tested

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the "unknown" extracts sent to them and submitted reports to Rockwell. From forty-eight different samples of house dust, twenty-four different extracts were made. A total of 365 patients were used for testing, and 3,224 individual tests were made, with controls. One interesting fact: no dust extract on the market, lot after lot, bottle after bottle, is exactly the same; for example, Rockwell tested two lots of Endo dust—one contained 0.46% mg. phosphotungstic acid precipitate, the other only 0.310.

The following conclusions were drawn: (1) No relation exists between skin reactivity and the total nitrogen. (2) Although some relationship exists between skin reactivity and the phosphotungstic acid precipitate, it is not too good when there is appreciable variation in the molecular size of the dust antigen. (3) But when extracts were selected whose antigens were of approximately the same molecular size, and when they were adjusted so that the phosphotungstic acid precipitate nitrogen was constant, their skin reactions were alike within limits of experimental error. (4) Not much discrepancy existed in skin reactivity between extracts of dust collected in various parts of the country. (5) Extracts which were purified and concentrated with alpha picoline, or by the absorbed method, are potent, better than crude extracts or any other extracts which were compared. (6) Successful standardization can, therefore, be done by combining chemical and biologic methods. The total nitrogen and the total and free alpha amino nitrogen of the phosphotungstic acid precipitate are determined. Such extracts should then be tested biologically and dilutions made based on their chemical analysis, namely, dilutions so that the extract contains 0.003 mg. phosphotungstic acid precipitate nitrogen per cubic centimeter. Such an extract should give positive reactions in a known dust-sensitive patient and negative reactions in normal individuals.

Brown and his co-workers<sup>17</sup> have a long and excellent review of the literature on the house dust antigen. The earlier results were at variance because the extracts were often very poor and skin testing was frequently associated with irritants. Therefore, passive transfer and constitutional reactions were infrequent. But since the work of Efron and his associates, a good reliable house dust extract is available, with excellent scratch test reactions in dust-sensitive patients, and with positive transfer and frequent constitutional reactions from injections. In other words, until a good dust extract was used, much of the earlier reports are not too important. Dust allergy is common and important, and, with avoidance and hyposensitization with good extracts, results are usually excellent. Barach<sup>21</sup> mentions dust hazard from concealed radiators; dust accumulates, and cleaning should be regular and thorough. Shambaugh<sup>22</sup> emphasizes the major role of house dust in causing chronic nasal and sinus symptoms, with superimposed infection; he obtains good results from injections of house dust extract. [We have noticed within recent years that some rhinologists have become overenthusiastic concerning the role of house dust. These workers should not forget that other allergens can and frequently do cause allergic rhinitis and sinusitis. In other words, tests should be carried out with all extracts which might possibly be factors, foods as well as inhalants.]

## FUNGUS ALLERGY

Deamer and Graham,<sup>22</sup> in a twelve-month survey of the atmosphere in San Francisco, found that *Hormodendrum* was the most common fungus; *Alternaria* spores were rare. Almost 60 per cent of the Petri-dish colonies were of the former, with only 2.4 per cent *Alternaria*; *Penicillium* colonies constituted over 19 per cent. There was no marked seasonal variation, and no great difference in plates exposed in the Marina residential district of San Francisco and those in Sacramento. This perennial character increases the difficulty in clinically detecting allergy to molds. Slides were also studied.

Reports also come from abroad. Nilsby<sup>251</sup> exposed plates for thirty minutes daily on the fourth floor of his home in Sweden from August to December, 1946. The greatest concentration of molds occurred at the end of August, decreasing during the defoliation period and increasing in misty weather. A few spores were present even in severe cold. Outdoors, *Hormodendrum* was the most common, followed by *Penicillium*, *Pullularia* and yeast-like fungi. Indoors, *Penicillium* was the leader and there were no seasonal fluctuations; colonies varied from 0 to more than 100 in one home. In another home, twenty-five colonies of *Alternaria* were found but this fungus is uncommon in Sweden. In other homes an almost pure culture of *Monilia tropicalis* was present. More fungi were found in rural communities than in the cities of Stockholm and Gothenburg. Spores were found in large numbers up to 200 meters, occasionally up to 700 meters (aeroplane studies). Very high counts occur in barns and threshing mills. Positive skin tests to mold

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extracts were obtained in 15 per cent of 276 allergic patients (chiefly those with asthma and chronic rhinitis).

Duarte Silveira<sup>166</sup> lists nineteen molds and many bacteria found in the atmosphere of Rio de Janeiro. Hyde and Williams<sup>176</sup> caught *Alternaria* spores by the slide method in Cardiff, Wales. The total count from June to September, inclusive, was 636 (89 per cent of all spores) in 1942, and 726 (96.5 per cent) in 1943. The highest counts coincided with the highest temperatures. Very few spores occurred in late autumn or in winter. The source of the *Alternaria* spores is thought to be cereals growing in the vicinity. In 522 asthmatic patients in England, Fraenkel<sup>120</sup> found that 849 gave positive skin tests with extracts of *Aspergillus*, *Penicillium* or *Mucor* fungi. Molds are much more important in England than on the European continent, due to the excess moisture in England and to the construction of British homes. *Sporotrichum*, *Cladosporium* and *Monilia* are also frequent. A survey of the air in Barcelona, Spain, revealed *Aspergillus*, *Penicillium*, *Cladosporium*, and *Alternaria* as the most important molds, according to Frouhman.<sup>128</sup>

Richerdtorf and Hampton<sup>100</sup> continued their studies of fungi in the San Antonio, Texas district, with special reference to skin tests. They found spores in the air almost daily, with high counts at intervals. *Hormodendrium* and *Alternaria* had the highest incidence by the plate method, *Alternaria* and *Helminthosporium* by slides. Significantly positive intradermal skin tests with mold extracts were found in 12.28 per cent of 186 patients; in thirty patients, mold extracts gave the only reactions. In 488 control individuals there were only six marked reactions with pseudopodia.

### POLLINOSIS

Jones<sup>187</sup> counted ragweed at Waterbury, Connecticut. His counts were very low, being 393, 275, and 273 for the entire 1944, '45 and '46 seasons. Hyde and Williams<sup>177</sup> caught ten times as many grass pollens on slides which were placed vertically to catch the impact of the wind, as compared with those caught by the ordinary gravity method. There was little difference in counts between slides exposed on the roof of a building or on the ground in the midst of grass.

Despite positive scratch test reactions to pollen in 10.5 per cent of sixty-three Brazilian asthmatic patients, and in 13 per cent of sufferers from rhinitis, Oliveira Lima<sup>211</sup> has found only one undoubted case of hay fever, a Spanish woman. There have been no reports of true hay fever in native Brazilians. Three pollen seasons were found in a survey of twenty-four cities in Brazil: (a) a grass season from mid-May to mid-June (chiefly *Melinis minutiflora*); (b) *Ambrosia polystachya*, in San Paulo in October, November, and December; and (c) a cypress season in San Paulo and Curitiba.

Morton<sup>246</sup> surveyed Toowoomba, Australia, over a period of nine years. Asthma and hay fever from weeds is usually associated with sensitivity to grass pollen; tree pollen is of little importance. There is no true differentiation of seasonal allergy into early, middle or late summer types. Meteorologic conditions are very important and vary from year to year. Cypress pollen sensitivity in South Africa was important in fourteen cases of Ordman.<sup>256</sup>

### MISCELLANEOUS CAUSES OF ASTHMA

Finland furnishes two reports of asthma in bakers. Kilpinen<sup>107</sup> found eight cases of occupational "eczema" in 653 bakers in Helsingfors, and four bakers had occupational asthma and/or rhinitis. Linko<sup>217</sup> studied 328 workers at bread factories, bakeries and pastry shops who came in contact with flour; sixty-six were clinically allergic to flour (about 20 per cent). Asthma and rhinitis were found in twenty, asthma alone in six, rhinitis alone in forty. Eosinophilia in the blood was found in nineteen cases. Exposure tests were positive in forty-three of fifty trials. "Family predisposition" was not decisive as regards genesis of allergy to flour. Symptoms developed on an average within eleven years after beginning work in a bakery, but in thirty-two cases, signs appeared before ten years. [Our impression is that similar allergy in bakers in this country occurs more quickly.]

Gum tragacanth which was present in a brand of Pyribenzamine tablets led to asthma and urticaria in a hay fever patient of Brown and Crepea.<sup>48</sup> The Pyribenzamine and the other ingredients in the tablet were not responsible, as shown by feeding and by scratch tests. Scratch tests were positive for gum tragacanth and closely related 1 per cent karaya gum, and tests by passive transfer and by neutralization were positive for tragacanth and negative to both karaya and acacia. The patient had been excessively exposed to tragacanth while working in a candy manufacturing plant. The authors rightly observe that "before ascribing sensitivity reaction to the main ingredient of a medication, the other constituents also should be investigated."

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Simon<sup>317</sup> notes the development of an allergen in wool. An eighteen-year-old boy had asthma for three years in the colder months, only at night, and only in his own home. He gave a 4-plus positive scratch test to an extract made from the comforter on his bed, with a negative control. Tests with wool from other sources, e.g., overcoat, glove, blanket and wool removed directly from a sheep, were all negative. The asthma ceased when the comforter was removed from the bed even though the patient continued to sleep in the same bed. [Perhaps a combination of mold and wool sensitivity may be responsible or an aging decomposition process.]

Friedlaender and Feinberg<sup>121</sup> found sensitivity to aspirin in forty-five chronic asthmatics (seventeen men and twenty-eight women). The onset of the asthma almost always preceded the discovery of the allergy to the drug. As expected in this type of asthmatics, chiefly middle-aged, skin tests were only positive in sixteen patients, with clinical improvement in only twelve of these. Eosinophilia, emphysema and nasal allergy with polyposis were commonly associated. The authors suggest that these aspirin-sensitive patients might also be allergic to some other simple chemical compound with resultant symptoms. "Such a mechanism could explain the many cases of allergic disease in which a specific protein allergen cannot be identified."

Other chemicals have been incriminated. Sulfathiazole powder caused typical asthma by inhalation in two nurses, as reported by Rosberg.<sup>291</sup> Epicutaneous tests with sulfathiazole were negative, but positive reactions were obtained with 2-aminothiazole hydrochloride (in both cases) and acetylsulfanilic chloride (in one case), substances probably formed by the decomposition of sulfathiazole in the body.

In ten asthmatic workers in the fur industry, Silverberg and Heimann<sup>315</sup> hold paraphenyldiamine (fur dye) responsible. Scratch tests with the dye were negative in all ten, but four gave positive reactions on patch testing with the dye (only one of these had a dermatitis). Patch tests on workers who had neither asthma nor dermatitis were negative. Here, then, is a paradoxical situation in that the shock tissue which reacted (epidermis) is not the one which reacted clinically.

Jamieson reports two cases also apparently due to chemicals. One patient, a provincial apiarist, developed asthma from bee scent,<sup>184</sup> and severe asthma developed within a minute after inhaling from a vial which contained bee scent dissolved in ether (three negative control vials of ether). He also gave positive skin and passive transfer reactions to an extract of bee wings, but when this extract was washed with acetone, skin tests were negative. Contents of the bee scent glands dissolved in huffer solution gave a marked positive reaction. This patient gave positive skin reactions to all members of the super-family of the *Apoidea*, but to no other members of the super-family of *Hymenoptera*.

A twenty-seven-year-old housewife<sup>185</sup> wheezed and coughed when changing wet diapers or washing them. Attacks always began in about two minutes and lasted about thirty minutes. The attacks were more severe if a stool was mixed with the urine. The patient also had asthma from flatus, heavy perspiration, Limberger and green cheeses, rotting seaweed and skunk odor. The family history was negative for allergy. By inhalation experiments, Jamieson proved that the attacks were due to the ethereal sulfates, the aromatic end products of protein metabolism as excreted in urine, feces, and sweat. The attacks from cheese are due to the acid formed by the propionic bacteria present in these foods.

Ordman, from South Africa,<sup>257</sup> reports thirteen cases of bronchial asthma due to inhalation of the dust resulting from the disintegration of the bodies of sewage filter flies (*Psychoda*). All patients worked at a sewage plant in the Transvaal. One case history is given in excellent style, including a strongly positive passive transfer reaction. In six cases, skin tests were positive, and in three of five, passive transfer was also positive. Control tests were negative in twelve non-asthmatic individuals. From East Africa, Reed<sup>280</sup> reports severe asthma and urticaria in a European who had been stung by a bee three minutes previously, with relief from asthma by epinephrin. Cattaneo and Alberici<sup>60</sup> report asthma for ten years in an Argentine woman, with associated urticaria, cephalgia and pains of the gall-bladder-colic type. Positive reactions for hydatid disease were found, along with 11.6 per cent blood eosinophilia and eosinophilia in the sputum, and with Charcot-Leyden crystals and Curschmann spirals. X-ray revealed a calcifying hydatid cyst of the liver. The patient was given the treatment of Calcagno: intramuscular injections of fresh human hydatid fluid, beginning with 0.50 c.c., increasing 0.25 c.c. every three days, with maximum dose of 7.0 c.c. and a total of 62.0 c.c., without notable reactions. The asthmatic symptoms disappeared, and she was still symptom-free ten months later.



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The factors which contribute to attacks of asthma, e.g., psychogenic and endocrine, will be discussed in the section on treatment (q.v.).

### PATHOGENESIS AND PATHOLOGY OF ASTHMA

A death from asthma<sup>22</sup> occurred in a boy aged twenty-two months. He was first seen at eleven months with "asthmatic bronchitis" which followed an upper respiratory infection two months before. He had had persistent rhinitis and an intermittent cough since the onset. The child was released from the Children's Memorial Hospital, Chicago, and readmitted a month later for bronchoscopic examination, with normal findings. At fifteen months the diagnosis was changed to bronchial asthma; skin tests were negative. They were repeated three months later by one of us (L.U.), and again all tests, including all dilutions of house dust, scratch and intradermal, were negative. Asthma continued despite a trip south, and he received many injections of epinephrine. His final admission followed rhinitis; terrific asthma ensued, with no relief from aminophylline, glucose, epinephrine, et cetera. Temperature rose to 107.2° F., with marked cyanosis, numerous wheezes, rhonchi, and death. Autopsy showed 100 to 150 c.c. of sterile fluid of unknown origin in each pleural cavity, with all branches of bronchi occluded by thick light green, tenacious mucus which by smears showed many eosinophiles; *B. coli* was isolated. Final anatomic diagnosis included: (1) marked mucopurulent bronchitis and bronchiolitis, (2) asthma (clinical), (3) bilateral hemothorax, (4) foci atelectasis, (5) compensatory emphysema, and (6) foci of pulmonary edema. As Unger suggested in his discussion of this case, the child might possibly have been helped by bronchoscopy in his terminal illness, but his condition when seen seemed too critical for even this procedure. [We have recently relieved coma twice in an elderly asthmatic patient who was too feeble to cough up her sticky sputum. Bronchoscopic aspiration was life-saving here, as it often is in other patients of this type.]

Lowance and his co-workers<sup>23</sup> present seven cases in which death in asthma was thought to be complicated by or caused by cardiac complications. Autopsy was done in one case, in which a thirty-eight-year-old patient with hay fever, asthma, positive skin tests and positive family history for allergy died in a doctor's office. The main findings were acute dilatation of the right side of the heart, marked emphysema, old pleural adhesion, and cholelithiasis. The pathologist said the patient died of right heart failure, plus active severe generalized emphysema. The heart was quite small, and the lungs bulged. No electrocardiogram had been done.

Autopsies were not done in the other six cases. Patient 2, aged twenty-nine, with asthma for two years and marked sinus and nasal involvement, and with repeated hospitalization, died in status asthmaticus. Patient 3, aged seventy-two had "asthma" plus cardiac decompensation, with negative skin tests. These cases and the others noted were believed to have cardiac complications in allergic asthma.

Love and Driscoll<sup>24</sup> injected 100 million anti-typhoid organisms intravenously in a twenty-year-old man with choroiditis. The temperature rose to 102° in twelve hours and was normal in three hours. A second dose (same strength) was given the next day; in one hour the temperature was 102.6° and rose to 107.2° F., with chill, tachycardia, vomiting of bloody material, hematuria, and a blood urea nitrogen up to 66 mg. Death occurred on the next day. Autopsy revealed generalized petechiae in the brain and parenchymal organs and massive necrosis of the liver and kidneys. Death was thought due to a generalized anaphylactoid reaction similar to that described by Sanarelli and Schwartzman in experimental animals. The authors believe that the unfortunate reaction could have been avoided if the interval between intravenous injections had been lengthened to forty-eight hours or more.

One of us (L.U.) has also recently had a similar unfortunate experience. The first dose of typhoid vaccine (10 million) was injected intravenously on the same day to three patients who were in the hospital for status asthmaticus. Two responded favorably with the usual chill, low fever, and temporary improvement in asthma. The third patient, a woman aged fifty-five, developed a chill, a higher fever than the others, diarrhea, collapse, and rather sudden death. Autopsy was urged but was refused. This is our first fatality with this procedure. There was no previous known typhoid fever nor injection of typhoid vaccine.

Death has followed injections of thiamine hydrochloride. Reingold and Webb<sup>25</sup> had given three large intravenous injections without serious reaction, but the fourth dose of the same strength led, within ten minutes, to generalized burning, profuse perspiration, dyspnea, cyanosis, and death. Autopsy showed constriction of the pulmonary arteries with engorgement of the lungs, right heart dilatation and failure, and mild emphysema. Death was thought due to allergy to thiamine. Sundelin<sup>26</sup>



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injected a thiamine preparation called Aneurin. The seventh intramuscular injection in his forty-year-old patient was followed by coma, wheezing, dyspnea, thready pulse, urticaria, diarrhea and vomiting, with recovery after a few days.

A death which may or may not have been associated with periarteritis nodosa is reported by Hill and Damiani.<sup>106</sup> Death occurred twenty-five days after inhalation of a spray containing a 6 per cent solution of DDT in kerosene. Marked asthmatic symptoms occurred, with progressively increasing dyspnea and cough with temporary relief from frequent injections of epinephrine. A severe generalized, pruritic, maculopapular rash was also present. There were 43,000 white blood cells with 20 per cent eosinophiles. Biopsy and autopsy findings suggested periarteritis nodosa.

Rifkin's twenty-four-year-old soldier was given 1.0 c.c. of typhus vaccine subcutaneously.<sup>285</sup> Sudden dyspnea occurred, with death within twelve minutes. There was no previous injection of typhus vaccine, but records did indicate sensitivity to egg. Autopsy revealed severe emphysema, marked eosinophilia in the bronchial secretion and the walls of the bronchi and bronchioles. The findings were attributed to tetanic contraction of the bronchial muscles with resultant emphysema and eventual asphyxia. Ratner and Untracht<sup>276</sup> have an excellent paper on allergy to Influenza A and B vaccine in children. In a group of 108 highly allergic children, 10.2 per cent were sensitive to egg white protein, but only 4.6 per cent were sufficiently allergic to cause alarm as regards injection of influenza vaccine. All persons should be tested intradermally with undiluted vaccine, using 0.02 c.c. before administering each and every dosage; if this test is negative or suggestive the vaccine can be given with impunity. A history of egg-sensitivity is not as reliable a criterion as is the intradermal test with the vaccine, say the authors.

Alhroon<sup>8</sup> reports death after a second local application of 2 per cent Pontocaine fifteen times the anesthetic power of cocaine and is two and one-half times as toxic. There is no known test to reveal sensitivity, and reactions seem to occur more often in allergic individuals.

Selle<sup>305</sup> discusses the physiologic basis of asthma. No one has actually seen bronchospasm through a bronchroscope but, of course, the terminal bronchi are not accessible to direct observation. Thickening of bronchial muscles does occur in some cases, but he favors the theory of occlusion by plugs of tough sticky mucus as commonly observed by such men as Raekenmann and Unger. While there is much evidence to substantiate the histamine concept, it is a fact that the so-called antihistaminic drugs like Benadryl are of little use in asthma.

Selye<sup>309</sup> has a very lengthy paper on the "General Adaptation Syndrome and the Diseases of Adaptation," with a tremendous bibliography. He is an earnest and enthusiastic worker, and we can all learn much from him. His alarm reaction is defined as "The sum of all biological phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted." The reader is urged to study his entire article.

An interesting note comes from an answer to a query in England.<sup>6</sup> There is no evidence that production of adrenaline is deficient in asthma, and the absence of signs of lessened sympathetic activity supports the view that there is probably no type of asthma caused by deficiency in secretion of adrenaline. The asthmatic reveals no pathologic changes in his adrenals. It is possible that psychologic factors which precipitate asthma may cause parasympathetic overaction and thus cause attacks. It has been noted, for example, that during conditions of prolonged fear in London, as in air raids, asthmatic patients have not had attacks in circumstances where attacks were expected.

H. Miller<sup>289</sup> of Los Angeles, in discussing the physiological basis for treatment of intractable asthma, points out that bronchial asthma is a proof of bronchial obstruction, regardless of the cause, and the most common causes are allergy and infection. The obstruction produced by the defense mechanism is due to bronchospasm, mucus plugging, and bronchial edema, and treatment must be based on a proper appreciation of each of these possibilities. [We would place bronchospasm as the third rather than the first factor.]

From France, Anglade<sup>14</sup> discusses voluntary apnea in normal and asthmatic children. The longer the child can hold his breath, the more nearly normal is the child. When there is diminution of voluntary apnea, another attack of asthma will probably take place in a few days. This method is excellent in noting improvement or lack of improvement.

Robinson<sup>289</sup> has a long article on "Stagnation of Tissue Fluid Is a Constant Pathologic Finding in Allergic Disease of the Nose and Paranasal Sinuses." Removal of this excess fluid by local pressure, as by balloons, tends to prevent nasal polyposis

and thus aids in preventing or relieving some cases of bronchial asthma which are related to sinus disease. The duration of relief varies.

Rackemann philosophically discusses some future problems in allergy.<sup>273</sup> Asthma which begins after the age of fifty-five is not the conventional asthma which starts in childhood. Allergy is not an important factor in the former group, but if an older individual has had asthma for many years, she or he is just as allergic as a youngster, and needs and deserves the same care in skin testing and injecting as is given the younger patient. This plea followed the report of death from skin testing in a seventy-eight-year-old patient who had asthma since the age of four. Intracutaneous tests were done without preliminary scratch tests.<sup>374</sup> [We have pounded on this point over and over again, yet conversation with physicians from all over the world reveals an alarming proportion who still do nothing but intracutaneous tests; a few more do some, but not complete, preliminary scratch tests. Along this line, the wholesale selling of sets for intradermal testing is dangerous and to be deplored.]

Confirmation of our point of view comes from Swineford.<sup>336</sup> A man aged forty-nine, with asthma for four years, gave a history of distension and burning from mustard, catsup, mayonnaise and cabbage, and of asthma and rhinitis from inhalation of hay, feeds, grains and house dust. Preliminary scratch tests with seventy-two commonly reacting allergens proved negative. Then intradermal tests were done with fifty-six foods and eight or nine inhalant extracts; the patient became ill and, despite heroic treatment, died within fifteen minutes. The skin tests showed very little because the man died very quickly. Autopsy was not done. In the second case, a woman, aged forty-nine, with asthma for fifteen years, had the asthma following onions, tomatoes and mustard and inhalation of several inhalants. Seventy-two preliminary scratch tests were also negative. Then about sixty-five intradermal tests were made, and thickness of the tongue, asthma, apprehension and delirium occurred quickly. Fortunately, large doses of epinephrine and aminophylline, followed by hospitalization, were successful. Later, scratch tests were done for all the injected food extracts, and a huge reaction occurred with the mustard-turnip-water cress group; the patient then recalled severe asthma and rash from mustard. No preliminary scratch tests to mustard had been made. The previous patient was the first fatality observed by Swineford in 7,000 patients who had been given intracutaneous tests after a preliminary set of seventy-two scratch tests. The author concludes: "Every intradermal test should be preceded by the less sensitive scratch test."

Harkavy<sup>155</sup> continues his writings on vascular allergy which were previously summarized.<sup>340</sup> Sensitivity to foods, pollens, sera, drugs, and bacteria may give various degrees of hyperergic reactions in the cardiovascular system. These changes are reversible at first if the offending agent is removed or corrected. Irreversible reactions, especially in the heart or kidneys, cause fatal cardiac or renal failure, as in seven of sixteen patients studied.

"A patient with long-standing asthma is under my care and contemplates a trip from Ohio to California. Would traveling in an airplane be harmful to him? Would the high altitude affect him in any way?" The answer to this query is excellent: "Asthma is not caused by anoxia nor is the usual attack of asthma associated with anoxemia. The latter phenomenon is discernible only in the severe stages of status asthmaticus. On the other hand, the high altitudes, owing in part to lesser amounts of airborne allergenic and nonallergenic irritants, lesser humidity and other conditions less easily understood, frequently improve the asthma. Unless the patient has cardiac decompensation, the altitude should not harm him."<sup>272</sup> [None of our patients has been harmed by high-altitude flights.]

Jacobs<sup>181</sup> cites experimental evidence regarding the importance of cilia in raising mucus; in fatal cases of bronchial asthma, an increase in goblet cells is frequent; this increase, plus damage to the cilia, leads to an excess of mucus difficult to raise. These factors, plus an upper respiratory infection which may destroy cilia, may lead to increased secretion and sufficient narrowing of the lumina to cause wheezing. Correct treatment of the infections, plus the use of potassium iodide to loosen the mucus, plus avoidance of narcotics, usually suffices to end the attack of asthma. Whooping cough, measles, and influenza can also damage the upper respiratory tract, especially in children, to an extent sufficient to cause outright asthma in a child who has a subclinical allergy.

In an excellent article, well illustrated, on pathology of asthma, Jiménez-Díaz and his associates<sup>189</sup> conclude that the obstruction is not due to bronchospasm. Rather it is essentially an acute congestion of the lungs with *ingurgitation* of the smaller circle through venous closing of the exit. In shock, by means of air, and in general, in slow shock, the congestive phase leads the way to another phase with arterial contraction and interstitial edema. Both the congestion and edema suffice to dilate

and hold rigid the alveoli. Attacks of bronchial and cardiac asthma are produced by the same mechanism, vascular or edematous ingurgitation, though the means differ. The best drugs, then, empty the smaller circle and suppress the edema.

Graña's article on "Hydatid Allergy"<sup>148</sup> is interesting. Some patients with hydatid cysts have asthma; others may have urticaria or angioneurotic edema (besides their nonallergic symptoms). He describes the Casoni and Pontano reactions, and notes blood eosinophilia up to 25 per cent in patients with cysts. If such patients receive injections of 1.0 c.c. hydatid fluid, a great increase in blood eosinophilia occurs in twenty-four to forty-eight hours. Typical crises of asthma occur in these cases, with benefit either from extirpation of the lung or liver cyst or desensitization with the hydatid fluid itself. Rupture of cysts may lead to anaphylactoid symptoms but "histamine apparently is not concerned with this type of shock."

## SYMPTOMATOLOGY OF ASTHMA

Tuft<sup>147</sup> has reviewed the subject of bronchial asthma from various aspects, including the gradual change which occurs in many cases from intermittent to chronic. He points out the frequent association of nasal allergy, and decries the wholesale surgery of the nose and sinuses which is now, happily, becoming a past epic. He, like us, dislikes the terms "intrinsic," "infectious," or "bacterial" as applied to asthma. He prefers to call them all allergic so that there will be an incentive to search for a possible etiologic factor. He likes the term "idiopathic." Old age is no bar to real allergy. A patient can be sensitive to foods, inhalants, and perhaps even bacteria in old age as in children. Better results in old age come from treatment based on the allergic point of view.

But Rackemann<sup>174</sup> still prefers the terms "extrinsic" and "intrinsic." He divides intrinsic asthma into six groups:

1. Asthmatic bronchitis, which may occur with "colds," and these patients may also be allergic to some extrinsic factor, e.g., dog or egg. Treatment must be directed against both the infections and allergic elements.
2. Vasomotor rhinitis, with negative skin tests, often in young adults, and often followed by severe asthma.
3. Bacterial allergy in older group of asthmatics. Environment and foods are not factors.
4. Depletion, when asthma is complicated by somatic factors, e.g., loss of weight and exhaustion, and by psychic factors, e.g., loss of morale.
5. Polypoid sinusitis with asthma. The nasal lesions are part of the picture, not the cause of the asthma.
6. Emphysema is a part of every attack of asthma but in the acute process is reversible. The chronic becomes irreversible.

Waldbott<sup>362</sup> asks "Is there an Intrinsic Asthma?" His answer is *no*. In a survey of 323 chronic asthmatics in 1,442 cases of asthma seen from 1942 to 1945, he was unable to see any real differences between this group and the rest of the asthmatics except that symptoms were chronic. It is true that "intrinsic" causes were responsible for attacks in many of these 323 patients, with influences such as sensitivity to cold, endocrine products (premenstrual aggravation), bacterial infection, and psychogenic factors. But "in no case were such intrinsic factors found to be the only causes to the exclusion of those termed extrinsic. The evidence indicates that there is no justification for the diagnosis of intrinsic asthma as a symptom-complex, and that the concept of such a syndrome may lead to faulty diagnosis and to abandonment of treatment at a time when treatment is needed and may be most effective."

We particularly like Waldbott's statement that "the most significant point brought out by Cohen (who favors the term 'intrinsic') is the utter hopelessness with which he views the existence of intrinsic asthma. He (Cohen) speaks of the waste of the physician's time and the patient's money if intrinsic asthma is not recognized. Such a conception (says Waldbott) is actually shared by many, perhaps by most, leading allergists. It cannot fail to have serious consequences. Indeed, I have seen patients in whom treatment has been abandoned because their asthma was defined by the physician as 'intrinsic.' Such an attitude by the physician necessarily creates a great deal of despondency on the part of the patient." [We may add that thorough skin-testing by both the scratch and intradermal methods will decrease the number of "non-reactors"; and a thorough history and examination will uncover some referred as asthmatics but who have other conditions, e.g., carcinoma.]

Hedström<sup>159</sup> discusses 1,250 asthmatic patients whom he has observed at the Åre

Mt. Sanitarium from 1923 to 1944. He recognizes the complex nature of asthma—an excellent paper, especially as regards handling of psychosomatic angles. Banchieri<sup>19</sup> discusses a case of bronchial asthma and divides the cases into those due to inhalation, to ingestion and those induced, as by overdose of antigen or by serum therapy.

There are three papers on vital capacity. Brown<sup>20</sup> and his co-workers studied forty-two hay fever patients over a period of two years; eighteen of these had simple ragweed hay fever, while the rest either had asthma or were sensitive to ragweed and other allergens. Vital capacity readings were made before and after August 11, chosen as the start of the ragweed season. Results: uncomplicated ragweed hay fever patients frequently show a lessened vital capacity during the season and most of these derive little benefit from injections of pollen extract. Variations in capacity are greater in those with multiple sensitivities. Intercurrent respiratory infections lower capacity, and pollen asthmatics have a lowered vital capacity even when they do not have clinical asthma.

Lowell and Schiller<sup>226</sup> did what Blackley tried on himself some eighty years ago [a rather dangerous experiment and not one to be recommended for general use]. Reduction in vital capacity to as little as 60 per cent of the original figure was obtained in each of six asthmatic patients who inhaled aerosolized extracts of birch, oak, grass and ragweed pollens. Cough, constriction of the chest, dyspnea, wheezing and hay fever occurred, as would be expected. The greater the asthma, the less the vital capacity. In all patients except one, the vital capacity returned to the control value within fifteen minutes, and the maximum degree of depression occurred six to ten minutes after inhalation.

Loeb<sup>218</sup> has an excellent article on physio-pathology in bronchial asthma. He gives thumbnail explanations of total lung capacity, ventilatory capacity, et cetera. His findings of abnormal respiratory patterns in asthmatic patients between attacks, in well-controlled experiments, are enlightening. He pleads for better understanding of allergy by the internist and for better knowledge in internal medicine by the allergist [Amen].

Asthma in children has not been neglected. Schwartz<sup>202</sup> stresses the importance of chronologic records in the management of allergic children. He devised a chart to indicate the occurrence of symptoms, the time of onset, frequency of attacks, location of symptoms, and possible changes in shock organs. In a boarding school, for example, a pupil whose symptoms occur December 21, March 28 and June 12 and who improves on returning to school is almost certainly allergic to something in his own home (pet?). Records are more dependable than memory.

Ratner<sup>277</sup> points out that asthma rarely begins before the age of three to eight, but frequent bouts of rhinitis usually precede the asthma. A careful history is very important; fever can occur in simple asthma but care must be taken to exclude infectious processes; skin tests should not be done until about a year has passed [we advise skin tests as soon as possible]. Scratch tests should always precede intradermal, and multiple sensitivity is the rule. Food sensitivity is not as important as inhalant (opposite to views of Chobot).

A questionnaire was sent to 338 children who had been hospitalized for bronchial asthma from 1926 to 1939. Replies were received by Flensburg<sup>117</sup> from 298 of these children, of whom 63 per cent were males. In 66.4 per cent the onset had occurred before the age of five, chiefly in the second and third years; in twenty the onset was during the first year, and asthma persisted. If "bronchitis" can be accepted as the criterion of onset of asthma, the average age of onset is considerably earlier. Replies showed that the attacks of asthma ceased in 40 per cent and recurred in 56 per cent. Death occurred in fifteen children (5 per cent), with status asthmaticus in five. No asthma was present in 41 per cent of the 131 children who reached the age of eighteen, and in 46 per cent of the 166 who had become twenty years old. Change in environment was the most important factor in clearing the asthma. But even in those who no longer had asthma, dyspnea on exertion was present in 44 per cent.

In England, where skin tests are much less thought of, and in fact, often laughed at or ignored, the results of skin tests are naturally disappointing. For example, Fisher<sup>124</sup> states that skin tests were practically negative, especially for inhalants and milk, in 200 children, of whom 48 per cent developed asthma in infancy, with onset in another 39 per cent between the ages of two and six. Respiratory infections, especially measles and whooping cough, frequently precede the onset, and it is often difficult, at first, to separate infectious symptoms from true allergic bronchial asthma. [A physician from India visited us recently. He said that he saw very little skin testing while he was in Great Britain and that practically none is done in India. We will gladly demonstrate patients and skin tests to visitors.]

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Rittwagen and his associates,<sup>288</sup> in a study of 100 children with rheumatic fever and 100 non-rheumatic children, report 33 per cent positive personal history and 31 per cent positive family history for allergy in the rheumatic group, and only 8 and 10 per cent, respectively, in the controls. Asthma occurred in 5 per cent of the rheumatic children, with hay fever in 2 per cent, food allergy in 12 per cent, and allergic rhinitis in 10 per cent.

Forman<sup>119</sup> courageously writes of asthma in the older group. Some are non-atopic, but he considers all as allergic until otherwise proved. His principles of treatment are in the section on treatment. [It is heartening to know that there are men who do not give up when elderly asthmatics are placed under their care. Much can be done.]

Brumm and Lons,<sup>12</sup> from Norway, have confirmed our belief that hyposensitization with specific allergens diminishes the size of skin test reactions, and that clinical improvement goes hand in hand with this lessening in the size of the skin tests. They did intradermal tests in seven different concentrations from 1:10,000 to 1:100 in 150 asthmatics. After hyposensitization, skin reactivity was diminished in 78 per cent, unchanged in 20 per cent, increased in 2 per cent.

Changes in the electrocardiogram during allergic shock are described by Castberg and Schwartz.<sup>62</sup> In animal anaphylaxis, changes in heart function are due to myocardial anoxia, not to allergic changes in the myocardium. In five hay-fever patients in whom constitutional reactions were occurring, with dyspnea (epinephrine withheld), tracings were similar. Tachycardia, P<sub>2</sub> increased, R1 and R2 decreased, T wave flattened in Leads I and II. In one case a positive T3 became negative. In three cases the S-T segment was depressed in Lead II. The P-Q, QRS and QT intervals showed very little change. A very low pulse during shock may be due to a vagus effect and deficiency tests. These changes are typically found in experimental oxygen may cause death unless 2 mg. of atropine are injected intravenously.

Heyer<sup>163</sup> reports as follows: (1) Pneumographic tracings of respiration revealed a similar type of distortion and prolongation of the expiratory phase in cardiac patients with pulmonary congestion and in patients with allergic asthma. Expiration in these patients did not undergo the relative shortening seen in normal persons. (2) During intravenous administration of aminophylline, the expiratory phase of patients with heart disease and asthma was promptly shortened, along with an abrupt and considerable increase in vital capacity. (3) The authors suggest that these changes in cardiac patients may be due to reflex bronchospasm induced by pulmonary congestion.

Asthmatics are subject to many complications, some serious. Febrile conditions are very common, and these include acute and chronic bronchitis, various types of pneumonia, and sinusitis, as well as other feverish conditions common to all individuals. Sodeman and Derbes,<sup>320</sup> in discussing the febrile asthmatic, state that the fever may be due to any one of the following: status asthmaticus with lung changes which they term "allergic bronchopneumonia"; Loeffler's syndrome, tropical eosinophilia; bacterial bronchitis; peribronchial pneumonitis, room inhalants, vaccines), and various intrathoracic diseases (e.g., tuberculosis and carcinoma).

Emphysema, which probably occurs in all chronic asthmatics, is discussed by Kahn,<sup>101</sup> who notes that treatment must be directed at the emphysema itself as well as the underlying asthma. Many of these patients are oversensitive and demand extra care as regards injections. Skin tests are frequently negative, yet, clinically, many of these patients are allergic to pollens and house dust and may obtain good results from hyposensitization. Such patients are not "intrinsic" or "infectious." Allergic rhinitis, sinusitis, and nasal polyposis are frequently associated. Polyps should be removed, but best results come from treating these patients meticulously from the allergy point of view. Kahn urges rest of the overworked lung, rest which should continue until exertion causes no dyspnea, this may require months, and is best carried out in the hospital at first, later at home. With this prolonged rest, as with chronic tuberculosis, gratifying results are obtained. Avoidance of allergenic factors as by filters, is important during this rest period. Kahn urges long rest periods after every attack of asthma; this will tend to prevent the onset of emphysema. Complete recovery after emphysema is well established cannot be expected.

Death due to spontaneous pneumothorax in a patient with chronic asthma is reported by Castleman.<sup>61</sup> Pneumothorax can also occur in tuberculosis, and in non-tuberculous and nonallergic individuals. Lombardi<sup>222</sup> reports such a case in an infant with subpleural blebs leading to multiseptate benign spontaneous pneumothorax.

*Subcutaneous* and/or *mediastinal emphysema* is comparatively rare; it can be caused by bronchial asthma or can occur independently. In children, Glaser states that only seven cases were reported up to 1941 as occurring in asthmatic children under ten. Largaia and Sojo<sup>207</sup> report subcutaneous and mediastinal emphysema which occurred in an eleven-year-old child during an attack of asthma. Precordial pain and dysphagia were prominent, and relief followed the use of morphine and codeine. The child also had tuberculosis [this means that the rupture may have been related either to asthma or to tuberculosis.] Another case occurred in an asthmatic five-year-old girl, as reported by the Children's Memorial Hospital, Chicago.<sup>235</sup> The child had been diagnosed as virus pneumonia, but the correct diagnosis was evident when typical crunching, bubbling sounds were heard over the precordium during cardiac contractions. This excellent paper also points out that x-ray characteristically shows elevation of the mediastinal pleura from the mediastinum and pericardium, producing a unique line on one or both sides of the mediastinal shadow. On the left this line is commonly visible above the pulmonary vessels and is due to the escape of air from the ruptured alveoli; the air travels along the vessels into the mediastinum. It is occasionally necessary to release air from the mediastinum (needle puncture, dissection through the neck, or splitting the sternum), but recovery usually occurs spontaneously. Creptitation, when and if the air reaches the neck, is, of course, diagnostic.

Schwartz and his associates<sup>301</sup> also discuss acute mediastinal emphysema. In excellent style, they report one case which occurred during an attack of asthma and hay fever, and six others which apparently were of spontaneous origin. They emphasize the typical crunching sound due to the thrust of the heart against air bubbles; this sound can often be better heard if the patient bends forward or lies on the left side. Five patients experienced a recurrence, and in two of these there were prolonged symptoms over six to nine months. All six spontaneous cases (not the asthmatic) had an associated spontaneous pneumothorax. They emphasize the necessity for careful examination of the precordium for mediastinal emphysema in all cases of spontaneous pneumothorax, especially if there is a small left apical pneumothorax. The best treatment is prolonged rest.

Van der Laan and Maresh<sup>356</sup> also report mediastinal and subcutaneous emphysema. A nineteen-year-old girl had such a severe attack that relief was only obtained after a "7.6 cm., low collar incision was made just above the sternal notch (local anesthesia). The muscles were separated in the midline, and a finger was inserted into the superior mediastinum through the suprasternal notch. There was an egress of air, and rapid improvement in the status of the patient followed. The subcutaneous emphysema disappeared gradually, and convalescence was uneventful." But their other patient was not so fortunate. A similar surgical procedure was necessary, but, despite some egress of air, death occurred nine hours after the operation and forty-eight hours after onset of symptoms. Autopsy revealed a "longitudinal linear rupture of the esophagus, 2 cm. long, just above the esophageal hiatus of the diaphragm." It communicated with a collection of foul fluid. The tear had evidently occurred in the course of marked vomiting and retching following consumption of a large amount of alcoholic beverages by the fifty-eight-year-old patient.

The relationship between bronchial asthma and *bronchiectasis* is not clear. The two can occur together, possibly independently. An asthmatic thirty-five-year-old man has been under the care of one of us (L.U.) for several years. He also had a very severe bronchiectasis of the left lower lobe, with some involvement of the right lower lobe, and with frequent bouts of pneumonia and pneumonitis. Since his left lower lobe was removed in May, 1946, his improvement has been remarkable. He still has occasional mild hay fever and asthma and is receiving appropriate injections, et cetera; but he has gained about thirty pounds, has had no further febrile attacks, and the râles which were present in the right lower lobe have disappeared. Lobectomy is by far the best treatment for bronchiectasis, if the patient is a fairly good surgical risk and if one has available an experienced chest surgeon. The condition can occur at any age, even in childhood. Diaz-Nielson<sup>91</sup> reports a case, proved by bronchiography, in a six-year-old boy, ill for three years following pneumonia. Cough and expectoration are the main symptoms. [Operation was not done, apparently, but should be carried out.]

Recurrent allergic parotitis, a rare complication, is reported in three asthmatics by Waldbott and Shea.<sup>363</sup> The swellings usually occurred just before onset of attacks of asthma. In one patient, swellings preceded the initial onset of asthma. Elimination of causative foods resulted in relief from swellings; therefore, recurrent parotitis may be allergic.

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### DIRECT DIAGNOSIS OF ASTHMA

Bronchial asthma is a condition rather easily diagnosed in most cases. Very little new material has appeared, and these chiefly on refinements and aids in diagnosis. For example, Dutton does not like Wright or Giemsa stains in examination of nasal and sputum smears.<sup>80</sup> He prefers eosin followed by alcohol acetone, then methylene blue—the whole procedure in about thirty seconds. The eosinophilic granules stain an intense pink, all other elements blue. Slides should be examined under low power first, else one may miss scattered patches of eosinophilic cells. Dutton<sup>80</sup> also suggests a rapid darkfield technique for examining sputum for bronchial spirochetes which may be responsible for chronic bronchitis, with or without asthma. Most cases are missed by the usual methods of examining sputum. The simple darkfield element (Bausch and Lomb) replaces the uppermost hemisphere of the Abbe condensing system. The spiral organisms, if present, are easily seen and identified. On several occasions, this routine method revealed spirochetes when not suspected.

The sedimentation rate and Weltman reaction in allergy may be compared. Parsons<sup>238</sup> did 3,000 sedimentation rates in one year in patients with various allergic and nonallergic conditions. The Landau-Adams apparatus was used and the results noted at end of one hour. When possible, tests were made on each patient throughout the year, with frequent tests in seasonal cases during their seasonal exacerbations. Normal was 1 to 10 mm.; infections were well over 25. Results were as follows: allergic migraine (nine cases), all 2 to 8 mm. except two who had temporary rise because of infectious complications; bronchial asthma (forty-five cases) (uncomplicated), 3 to 10 mm.; allergic bronchitis (nine patients), seven normal at start, with the other two at 20 and 26 mm. which returned to normal when the complicating infection was gone. Other allergic conditions were studied, and Parsons states that examination of sedimentation rates is very helpful in differentiating allergic and nonallergic conditions, and has avoided unnecessary allergy diagnostic procedures, on the one hand, and explained some failures, on the other hand. A high rate calls for search for infection. The percentage of error is small (5 per cent).

The procedure should be routine. Dutton,<sup>80</sup> on the other hand, prefers the Weltman reaction as a diagnostic aid, and calls attention to Dees' paper (1941), which first told of the value of this test in allergic diseases.<sup>84</sup> The technique is simple, and Dutton says the test is even more dependable than the sedimentation test in indicating an infection. It is easily applicable for use in a small laboratory and deserves a wider use.

A rapid and accurate technique for counting blood eosinophilia is described by Discombe.<sup>93</sup> one part of blood is diluted with twenty parts of staining fluid (five volumes each of 1 per cent aqueous eosin Y and of acetone and ninety volumes distilled water). The pipette is shaken vigorously. A normal eosinophile count is 0 to 240 per cubic millimeter. A mild eosinophilia (400 to 500 cells) was found in most quiescent asthmatics.

The usefulness of the leukopenic index estimation as regards allergy to foods is by no means dead. Several allergists in this country continue to use the method, and their experience and care in technique yield good results. In Norway, Lindeberg-Luidnet<sup>216</sup> obtained better results in two food-sensitive asthmatics by this method than by any other, including tests with food extracts.

To determine whether an x-ray shadow of maxillary sinus opacity is due to chronic infection or allergic edema. 0.5 to 1.0 c.c. of 1:1000 epinephrine is injected subcutaneously. Frouchtman and Ferrando,<sup>129</sup> in eight cases of allergic sinusitis, showed that the epinephrine lessened opacity as demonstrated by x-ray; the opacity is due to edema of the sinus mucosa, and this edema is reversible. In chronic allergic sinusitis with fibrosis, epinephrine reduces the mucosal edema but cannot entirely clear up sinus opacity.

Vilhena<sup>358</sup> emphasizes the importance of examination in asthma of sputum, nasal smear, blood, and other laboratory procedures, including search for fungi, bacteria, worms, and a tuberculin reaction. Millman<sup>242</sup> also discusses the diagnosis and differential diagnosis of respiratory allergy.

### BRONCHOSCOPY IN DIAGNOSIS AND TREATMENT

Because of the growing importance of the bronchoscope in the differential diagnosis and treatment of asthmas, it was thought best to gather the literature on this subject in one section. A good bronchoscopist is an invaluable aid. One of the finest of all papers is that by Lell<sup>211</sup> on "Bronchoscopy in Diagnosis of Allergic Pulmonary Disease." In 176 children examined bronchoscopically because of "asthma," 130 really had bronchial asthma. The others were: eighteen with



foreign bodies in the respiratory tract, five with foreign bodies in the esophagus, fourteen with tracheal compression, one with retropharyngeal abscess, and eight with organic changes in the larynx itself.

In 102 patients with status asthmaticus, 269 bronchoscopic examinations were made, and the pathologic findings were uniformly consistent: hemorrhagic and redundant mucosae greatly lessened the size of the lumina of the trachea and bronchi; thick tenacious secretion was always present; and, on expiration, collapse of the posterior wall of the trachea was always seen. These changes were confirmed in gross and microscopic studies in five patients who died in status asthmaticus. [Readers are urged to study this article.]

Holinger and Kirby<sup>18</sup> also have a fine article, with presentation of three cases. One patient had complete bronchus obstruction by a screw with resultant atelectasis and bronchiectasis. The second had mediastinal, pericardial and subcutaneous emphysema from a check-valve obstruction of a bronchus by a peanut. In the third case, a metallic foreign body partially obstructed a bronchus with no signs except localized wheezing.

They also point out that increased negative pressure on inspiration harms for the following reasons: (1) It leads to an increase in pulmonary capillary blood pressure with transudation of serum into alveolar spaces. This is a direct result of the increased negative pressure on the heart and circulation, which increases the return flow of blood to the heart so that blood flow through the chest is increased, with more blood in the left ventricle. As the negative pressure rises, these two effects increase until there is a progressive accumulation of blood in the lungs; this causes a rise in capillary blood pressure with resultant congestion, transudation and pulmonary edema. (2) Exudation of fluid into the alveolar spaces and bronchioles occurs because of the suction action of the intrabronchial and intra-alveolar negative pressure. (3) A vicious circle ensues; there is a further increase in negative pressure due to the attempt to compensate for the effects of the other two actions by increasing the respiratory effort.

Blake<sup>23</sup> points out the usefulness, in fact the necessity, in many cases of bronchoscopy in the diagnosis of the lesions which may involve the tracheo-bronchial tree, e.g., pulmonary tuberculosis, adenoma, carcinoma, foreign body, postpneumonic atelectasis or abscess. Unilateral bronchiectasis may heal after opening of an obstructed bronchus, and bilateral bronchiectasis may be improved by periodic bronchoscopic aspiration. Contrary to popular opinion, foreign bodies are the reason for less than 5 per cent. of all bronchoscopic examinations. Kernan<sup>196</sup> also emphasizes the usefulness of the bronchoscope; aspirated secretions can be studied and can be used for autogenous vaccine therapy; the procedure is invaluable in differential diagnosis from bronchial asthma.

Kimér,<sup>287</sup> from Norway, aspirated material from the bronchi of twenty-six patients and instilled penicillin and/or sulfathiazole. These patients had such conditions as chronic, often purulent bronchitis, bronchiectasis, bronchostenosis and/or atelectasis. In all, the bronchial mucosa was congested and edematous, with sticky, gelatinous and tenacious secretion. Kimér says that the bronchial musculature was *spastic*. [This is not the finding my most bronchoscopists.] The bronchial secretion was sterile in only four of these twenty-six patients.

Hansen and Smidt<sup>154</sup> point out the value of bronchoscopic aspiration in preventing death in severe status asthmaticus—this by diminishing the tension of bronchial muscles and by removal of thick tenacious obstructing secretion. Deller,<sup>87</sup> from London, emphasizes the infectious etiology of bronchial asthma almost to the exclusion of allergy. He also finds bronchospasm forming a transverse slit at the bifurcation of the small tubes with resultant wheezing and dyspnea. Much tenacious sputum is seen, and the mucosa is swollen. He instills penicillin into the trachea and has patients inhale penicillin. These procedures plus aspiration lead to "temporary cures" in 78 per cent. [Deller's statement that he saw bronchospasm without doubt in over 100 attacks of bronchial asthma certainly needs verification; we also deplore his use of morphine in the treatment of bronchial asthma.]

## DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

Glaser's article<sup>141</sup> on differential diagnosis of bronchial asthma in infancy and childhood is excellent. Unger's definition is not complete, says Glaser, who suggests that "Bronchial asthma may be defined as a form of obstructive emphysema of allergic origin, involving both lungs throughout, characterized by paroxysmal attacks of dyspnea, chiefly expiratory, accompanied by wheezing heard on auscultation of the chest and typically relieved, at least in the early stages of an attack, by sympathomimetic drugs. The pathological physiology consists of edema, increased secre-



tion of the mucous glands, spasm of smooth muscle, and usually a local tissue and fluid eosinophilia." This definition emphasizes that bronchial asthma is only one form of obstructive emphysema, though the most common form. All "nonallergic asthmas" are other forms of obstructive emphysema and should be so designated.

[We must remark that the above definition is not entirely correct because (a) mild attacks of true bronchial asthma are hardly emphysematous; (b) true asthma is not necessarily paroxysmal; many are chronic from onset; and (c) "cardiac asthma" is one form of asthma certainly not associated with emphysema.]

Glaser sees about four to six cases of bronchial asthma each year in infants under one, but most develop at four to five. The classical sequence is: colic, usually at three weeks; atopic dermatitis a few weeks later; recurrent upper respiratory infections at two to three, followed by hay fever or allergic rhinitis, then asthma. This progression is typical but not invariable. Asthma in children, especially at two or less, differs from adult asthma in four respects: (1) dyspnea is not necessarily expiratory; (2) orthopnea may not be present; the infant can often lie comfortably even on his back; (3) infants rarely show anxiety; and (4) fever is common, though rarely more than 1.5° F.

He uses epinephrine in small doses: under one, 0.10 c.c. to begin with, followed by 0.15 c.c. in fifteen to twenty minutes, if necessary; this is repeated if asthma is still present. He occasionally uses small doses of morphine, though he prefers demerol or dilaudid. [We object to opiates].

Bronchial asthma, says Glaser, must be differentiated from many conditions: (1) Asthmatic bronchitis is characterized by coryza, fever, poor response to ephedrine or epinephrine, preponderance of neutrophils in nasal smears, and increased sedimentation rate. It may not be followed by bronchial asthma. (2) Foreign bodies in a bronchus are not uncommon; x-ray and bronchoscopy are mandatory if any possibility. (3) Cystic fibrosis of pancreas (case report with autopsy findings) has as chief symptoms the absence of good response to epinephrine and ephedrine, and of eosinophilia; failure to absorb glucose properly as shown by glucose tolerance curve; poor absorption of vitamin A as indicated by vitamin A tolerance test; diminution or absence of pancreatic enzymes on duodenal drainage. (4) Thymic asthma is rare, but may be helped by roentgen therapy. (5) Ayerza's disease is also rare (case report); chief symptoms are dyspnea, polycythemia, chronic cyanosis, prominent pulmonary conus with hypertrophy right ventricle, and right ventricular preponderance on electrocardiogram. (6) Dust bronchitis, previously noted in Dust Bowl, is due to inhalation of finely pulverized dust; cough is explosive, intractable, and non-productive, and fever and wheezing may be associated, with soft patchy mottling on x-ray. (7) Sighing dyspnea is a functional disorder. (8) Cough of whooping cough is characterized by no response to ephedrine or epinephrine, absence of eosinophilia, leukocytosis with relative lymphocytosis, positive culture for *H. pertussis*, no wheezing on forced expiration, and typical "whoop" which usually comes in three weeks. (9) Bronchotetany is rare, but dyspnea and wheezing may occur. Calcium intravenously gives brilliant results. (10) Cardiac asthma does not occur in infancy and childhood (White's youngest patient was eighteen, though Clausen reported cases at ages of eleven and twelve).

Chobot<sup>66</sup> has another paper on asthma in children. He does not like the term "asthmatic bronchitis." In his differential diagnosis he includes foreign bodies, whooping cough, transient pneumonias, bronchitis, lung tumors, tuberculosis, Loeffler's syndrome, and cardiac asthma.

Other articles deal with conditions which can simulate bronchial asthma. Frank's patient,<sup>122</sup> aged sixty-two, had a laryngeal carcinoma, but this did not initiate "asthmatic" attacks until roentgen treatment led to severe arytenoid edema with resultant partial obstruction of the larynx. Tracheotomy was necessary, and this relieved the obstruction, with cessation of "asthmatic" attacks. Holley<sup>169</sup> studied thirty-nine cases of bronchial adenomas. The predominant symptoms are cough, hemoptysis, expectoration, and recurrent acute respiratory infections. Lobectomy or pneumonectomy, depending on the location of the tumor, is the preferred treatment.

Bronchogenic carcinoma, says Van Ordstrand,<sup>350</sup> is now the third most frequent type of primary neoplasm, especially in males fifty to sixty years old. Seventy per cent originate in the central third of the involved lung, at or near the hilum in the main stem bronchus or its major bifurcations; therefore, visualization is possible in about sixty-five per cent of the cases, and early bronchoscopy is essential. Cough with or without hemoptysis is an early symptom, frequently followed by partial or complete bronchial occlusion with possible atelectasis, pneumonitis or lung abscess. In the average patient symptoms were present for seven months prior to correct diagnosis. Van Ordstrand urges bronchoscopy and x-ray in any patient who

has an unexplained cough for more than six weeks. He also urges exploratory thoracotomy if there is a unilateral wheeze, yet x-ray and bronchoscopy are negative.

Isaacson and Rapoport<sup>180</sup> note the occurrence of eosinophilia in carcinoma, an abnormally large number of eosinophilic cells in the blood stream may indicate metastases. Disseminated growths were found in twenty-seven of thirty-four cases of eosinophilia with carcinoma. [We have recently had a forty-one-year-old patient, referred for asthma, who had inspiratory instead of expiratory dyspnea. Despite the finding of 2, 80, and 100 per cent sputum eosinophilia, laryngoscopy and biopsy revealed squamous-celled carcinoma at the carina, with almost complete obstruction of both primary bronchi.]

Progressive bilateral bullous emphysema was observed in eight men during a three-year period by Price and Teplick.<sup>265</sup> The process begins in the apices and gradually increases in extreme cases until both upper and lower lobes are replaced by large cyst-like areas. Cough, slowly increasing dyspnea, recurrent respiratory infections, cachexia, and asthmatic attacks are the main symptoms, with death when insufficient pulmonary tissue remains, or from intercurrent infections. The etiology is unknown, but this condition may be similar to giant bullous emphysema, cystic disease of the lung, multiple cysts of the lung, cystic degeneration of the lungs, and vanishing lungs; these names have been given in cases previously reported. In all of these patients, similar features and x-ray findings are found, and in nearly all, the pulmonary conus of the heart becomes enlarged, with right heart strain. There is no effective treatment. Klosk and his co-workers<sup>189</sup> also write on "Cystic Disease of the Lung," with a report of twelve cases. Hemorrhage, infection, and spontaneous hemopneumothorax or pneumothorax occurred in the nine congenital cases. In three cases the condition was acquired and was associated with chronic bronchitis, peribronchitis, pulmonary fibrosis and "bronchial asthma." [In the three acquired cases associated with asthmatic symptoms, we believe that this is not a true cystic disease, but is merely bronchial asthma complicated by extensive formation of emphysematous bullae, a not infrequent finding; rupture may occur].

Alemaný Vall, from Barcelona,<sup>11</sup> points out that pulmonary tuberculosis can cause an "asthmatic" condition, and in some cases the similarity is striking.

Industrial dusts may cause lung changes. Wegelius<sup>368</sup> found 126 cases of asbestosis among 476 workers of the Finska Mineral Co. By x-ray, the condition was mild in ninety-four, moderate in twenty-three, and advanced in nine. The rather high percentage of advanced cases, as compared with statistics from other countries, is probably due to the recent recognition of this disease in Finland. Cardiac enlargement was less frequent than noted in other reports. Greenberg<sup>140</sup> found advanced fibrosis in thirty-two male workers in a group of tremolite talc miners and millers in northern New York State. All had worked with this talc for at least ten years; and in this group of 107 exposed that long, the incidence of fibrosis was 29.9 per cent. The fibrosis was of a fine diffuse type with the x-ray appearance of granulation or nodulation on a hazy background. Disability, with dyspnea, cough, and fatigue, was prominent, along with increased susceptibility to tuberculosis. In addition to fibrosis, "talc plaques" were observed in the lungs of 6.3 per cent of all those exposed. Tremolite talc, says Greenberg, is a silicate dust capable, like asbestos, of causing a disabling pneumoconiosis.

In a similar study of 344 workers, inhalation of particles of alumina abrasives (bauxite) caused symptoms, says Shaver and Riddell.<sup>311</sup> Radiologic evidences of disease were found in thirty-five, with thirteen others classified as doubtful; fatality had occurred in seven. In several, the condition has progressed rapidly, with severe disability. The acceleration demanded by the war apparently was a major factor in increasing exposure, and cases observed in Germany seem to have occurred under similar circumstances of increased production. The disease is essentially an interstitial lung fibrosis, non-nodular in type, but may be associated with severe emphysema, with blebs and rupture with spontaneous pneumothorax. The process involves inhalation of alumina and silica, both in a very fine state of division, and of small quantities of many other substances.

*Cor pulmonale* very possibly results from similar pulmonary conditions, not all of them fibrosis, however. It certainly occurs very rarely in an uncomplicated bronchial asthma, no matter what the duration, even in those chronic asthmatics in whom emphysema is fairly severe. Spain and Handler<sup>323</sup> have an excellent paper on this subject, based on a series of sixty consecutive cases studied at necropsy. Those cases were selected in which there was no significant evidence of hypertension, valvular heart disease, congenital lesion, syphilitic cardiovascular disease, or coronary atherosclerosis, but with hypertrophy of the right ventricle. Underlying pulmonary conditions were emphysema in forty cases, bronchiectasis in six, bronchial

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asthma in six, silicotuberculosis in three, pulmonary tuberculosis in two and one case each of kyphoscoliosis, pulmonary arteriosclerosis, and organized pulmonary thrombi. The authors discuss the role and methods by which each of these conditions can produce cor pulmonale. Errors in diagnosis are common: in about fifty per cent, arteriosclerotic heart disease is diagnosed. The main diagnostic findings in cor pulmonale are increase in size of the heart to the right, prominence in epigastric pulsation, accentuation of pulmonary second sounds, fluoroscopic and x-ray findings, and right axis deviation in the electrocardiogram.

From Madrid, Bozal Urzay and Diaz Opacio<sup>41</sup> reviewed sixty-nine cases of chronic cor pulmonale and two of acute. The acute cases, both fatal, came after abdominal surgery. Occupational exposures were important causes in thirty-five of the sixty-nine chronic cases (jute and blanket workers, miners, millers). Cough, dyspnea, cyanosis, and low blood pressure were frequent. Electrocardiograms revealed bradycardia, low voltage, ventricular complex of small amplitude and right predominance. Roentgen studies showed enlarged hearts, especially of the right side. Treatment is removal from dusty occupations, change of climate, and guarding against infections. In patients without decompensation the respiratory symptoms usually disappear following improvement of the circulatory system (rest, digitalis, mercurial diuretics, et cetera).

There are several articles on the differential diagnosis of asthma from heart disease. Oliveira Lima<sup>253</sup> advises determination of venous pressure, circulation time, radiography, et cetera. "Cardiac asthma" shows evidence of left ventricular strain or failure, e.g., hypertension with aortic valve defect, with prolonged circulation time, and associated diminution in minute volume and accumulation of metabolic products by anoxemia and embarrassment of respiratory center. Rutledge<sup>259</sup> speaks of cardiac dyspnea and the methods for determining its existence. He stresses differential diagnosis between cardiac and bronchial asthma. From Ukraina, Mikheev<sup>257</sup> states that World War II afforded an excellent opportunity for studying cardiac asthma. The pathogenesis includes increased venous pressure, decreased vital capacity and velocity of circulation, and increased mass of blood in the pulmonary circulation with a corresponding decrease in the minute volume of blood. There is arterial and venous anoxemia.

Plotz<sup>263</sup> in a discussion of the mechanism of wheezing sometimes found in heart disease, concludes: (a) bronchospasm is an important element in certain types of heart disease; (b) cardiac asthma may occur with asthmatic wheezing and without basal râles; such cases are indistinguishable by physical signs from allergic bronchial asthma and may, like true asthma, be benefited by epinephrine; (c) epinephrine does not increase vital capacity in normal individuals; (d) epinephrine leads to sharp increase of vital capacity in patients with cardiac failure who wheeze but do not have basal râles, but (e) there is no effect in patients with basal râles; (f) expiratory pressure is sharply decreased in pulmonary congestion or wheezing conditions, and the expiration time is prolonged.

Bercovsky and Neuman<sup>27</sup> studied fifty-one cases with mitral stenosis or mitral disease with paroxysmal dyspnea; auricular fibrillation was associated in some. Sudden pulmonary stasis in such cases appears to be due to (1) shortening of diastolic filling time of the ventricles and decrease in circulation to the ventricular muscle itself originated by tachycardia, and (2) greater relative obstruction of the mitral orifice caused by an increased venous return to the heart.

Fungi can cause pulmonary disease which may simulate bronchial asthma. It is important to search the sputum, as already pointed out by Dutton. Smith<sup>259</sup> has a fine forty-page article dealing with the various fungous infections of lung tissue. These include actinomycosis, blastomycosis, coccidiomycosis, cryptococcus (torulosis), moniliasis, geotrichosis, sportotrichosis, histoplasmosis, aspergillosis, penicilliosis, mucormycosis, and infections of the lungs by *Bacteroides necrophorus*, *Actinobacillus lignieresii*, a peculiar form of staphylococcus, and spores of *Coniocorium corticale*, from exposure to the inner bark of maple logs.

Kunstadter and his associates<sup>263</sup> state that the symptomatic, radiologic and clinical findings of pulmonary geotrichosis are similar to those of other mycotic diseases. Such cases may simulate chronic bronchitis, bronchial asthma, pulmonary tuberculosis, and atypical pneumonia. Tuberculosis may coexist, but in any patient who apparently has pulmonary tuberculosis, with repeated negative sputa for tubercle bacilli, careful search should be made for fungi, and a therapeutic test with iodides will give good response in fungous cases. Sputum in such cases is typically white, mucoid with grayish flakes, and with a yeast-like odor.

Clark and Gilmore<sup>68</sup> injected a 1:100 coccidioidin extract into 372 individuals; positive reactions appeared in 125 cases, with negatives in all persons who had not

been in areas endemic for *C. immitis* infection. The positive skin test disappeared when two patients became very ill with the disseminated form of the disease. Complement fixation and precipitin antihodies for coccidioides may be found in blood, spinal and chest fluids in active stages of the disease. The skin test is similar to that with tuberculin.

A patient of Hitt and Martin<sup>161</sup> had severe pulmonary moniliasis and failed to respond to the usual treatment (iodides and intravenous injections of gentian violet). Skin and agglutination tests were negative for *Candida albicans*. An intracutaneous test with *anti-Candida albicans* rabbit serum was strongly positive, with a negative control. Subcutaneous injections of this serum caused dramatic recovery, following which the agglutination test for the fungus was positive in 1:80 dilution. The skin test became slightly positive for a short time.

Rifkin and Eberhard<sup>256</sup> report a South Pacific island native whose clinical history, x-ray and laboratory findings suggested the diagnosis of pulmonary filariasis. Numerous microfilariae characteristic of *Wuchereria bancrofti* and many eosinophiles were found in the sputum and peripheral blood. Skin test with *Dirofilaria immitis* antigen was positive in 1:8,000 and 1:16,000 titres.

Histoplasmosis is discussed by Zwercing and Palmer.<sup>381</sup> The pulmonary calcifications found on x-ray in persons who live in the east-central part of the United States are more often associated with a positive reaction to histoplasmin than to tuberculin. This confirms previous work of Palmer who surveyed student nurses in eight large cities. The positive reaction to histoplasmin, therefore, probably indicates a previous infection which, contrary to earlier beliefs, is not necessarily fatal. Histoplasmosis is probably widespread, and the pulmonary calcifications which it produces closely resemble those of pulmonary tuberculosis. The incidence in negroes is even higher than in whites.

## THE TREATMENT OF BRONCHIAL ASTHMA

The *specific treatment* of bronchial asthma is discussed in all the new books and is mentioned in many of the general articles. But only two papers deal with specific treatment. This paucity continues to be an astounding fact, and probably indicates that the two pillars of this type of therapy, avoidance and hyposensitization, are now pretty well standardized. One must never forget that the highest percentages of clinical cure (relief from symptoms) and improvement occur in those fortunate patients in whom the cause can be found and eliminated or, at least, minimized by hyposensitization.

All other methods of treatment are symptomatic, and the large number of papers on these nonspecific measures, e.g., antihistaminic drugs and various methods of inhalation therapy, make us wonder whether we are not departing too much from that narrow and straight path of specific treatment. In our enthusiasm for newer drugs and newer techniques, we must not forget that if one can prevent exposure or minimize it, these new drugs and procedures will not be necessary. This does not mean that the recent progress along these lines is not helpful; it is of great aid in many allergic patients, but we must not forget the principles on which the whole success in the field of allergy is based, i.e., the search for and removal of the cause, where possible.

Goodman<sup>146</sup> stresses the necessity of removing the offending substance as thoroughly as possible. He has four essential rules in his program of desensitization: (1) the solution contains the major reacting allergens, i.e., he mixes pollens, dust, dander, molds and vaccines in one vial. [we always separate tree, grass, ragweed pollen extracts, and vaccines]; (2) he begins with a dilution which will not cause a local or systemic reaction; (3) the dosage is progressively increased until a fairly concentrated solution is given without reaction; and (4) the patient's tolerance is then maintained by injections at regular intervals. Causes for poor results include (a) stopping treatment too soon, (b) interruption of schedule of injections, (c) continuation of contact with allergens, (d) failure to discover all responsible factors, (e) active foci of infection, especially in upper respiratory tract, and (f) situational factors, e.g., asthma may be convenient for some persons and may serve a purpose which makes the patient reluctant to part with it.

Von Dishoeck and Klein<sup>361</sup> studied inhibiting antibodies. During hyposensitization with grass pollen extract, an increase in the reagin titer of serum occurred before the development of the inhibiting antibodies; these latter were also demonstrated in sera of patients treated with injections of extracts of tobacco, orris root, beans, and wheat, but never with house dust despite good clinical results in dust-sensitive patients. Although high dosage and high inhibiting antibody titer seemed to corre-

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late with good clinical results, satisfactory relief was often obtained in complete absence of this antibody.

### ANTIHISTAMINIC DRUGS IN TREATMENT OF BRONCHIAL ASTHMA

There is a veritable flood of papers on the use of the so-called antihistaminic drugs in the various allergic diseases. Most of these new drugs relieve nasal congestion and pruritus, but have not been of particular help in bronchial asthma. We deal here with these drugs as applied to asthma; most of the reports are on Benadryl and Pyribenzamine, but reports on newer drugs are beginning to appear.

An interesting paper comes from Curry.<sup>80</sup> Histamine itself was injected intramuscularly and intravenously. There was no effect in ten normal persons nor in ten allergic patients, including asthmatics, who were free from asthma at the time. But in patients with varying degrees of chronic bronchitis, emphysema and asthma, histamine caused bronchoconstriction and lessened vital capacity in eight of nine cases. The degree of constriction was closely correlated with the dose of histamine, but varied somewhat with the patient and the severity of the asthma. During any single period of observation the same degree of constriction of the bronchi could be produced by identical amounts of histamine; the height of the reaction was thirty seconds by vein, two to three minutes by muscle. If given sublingually or by nebulization, there was definite but less pronounced constriction.

Loew and his associates<sup>219</sup> in guinea pigs, produced bronchoconstriction by exposure to atomized histamine solutions. The counteracting drugs, in order of efficiency, were epinephrine, Benadryl, Demerol, atropine, papaverin, and aminophylline. Epinephrine, morphine, pentobarbital, Transentine, Pavatrine and Syntropan were ineffective. Benadryl has received much attention. Levy and Seabury<sup>215</sup> studied the pulmonary volume, respiratory rate, minute ventilation, oxygen consumption, and ventilator equivalent of sixteen patients with "extrinsic" asthma, both before and thirty and sixty minutes after ingestion of 100 mg. of Benadryl. The drug caused no consistent change in any of the measurements, though six patients were clinically improved. Five patients who received 0.3 mg. epinephrine and 0.25 gm. aminophylline showed a uniform effect characterized by increased vital capacity, tidal air, minute ventilation, and expiration differential, with no increase in rate of respiration.

Bowen<sup>220</sup> was greatly disappointed, despite reports from Parke, Davis investigators, in which 63.5 per cent improvement was claimed in studies of 343 asthmatic cases. Benadryl helped less than 10 per cent of cases of bronchial asthma. Logan<sup>220</sup> reports improvement in six of seven children treated for single attacks of asthma, and in sixteen of seventeen children who had multiple attacks. He favors the combination of iodides and Benadryl in nonseasonal asthma. Todd<sup>344</sup> obtained complete relief from 450 mg. per day. Todd<sup>344</sup> obtained complete relief in four of eighteen patients with asthma, with partial relief in two and partial in three. Waldbott<sup>364</sup> found Benadryl unsucessful in sixteen of thirty pollen asthmatics and in twenty-four of forty-eight cases of perennial asthma. One seven-month-old infant obtained excellent relief from severe asthma following 50 mg. Benadryl, but in three patients severe attacks of asthma followed the drug. Symptomatic relief occurred in eight of twenty cases of asthma, as reported by Schwartz and Levin.<sup>306</sup> S. J. Levin<sup>213</sup> gave 50 to 100 mg. every four to six hours, with maximum of 300 mg. several times daily, with 5 to 20 mg. dosage in children. He found Benadryl practically useless when a respiratory infection either caused the attack of asthma or complicated it. Improvement occurred in ten of fifteen asthmatic children, and in forty-seven of seventy-two asthmatic adults, with aggravation of asthma in four patients.

From the Mayo Clinic, improvement occurred in fourteen of nineteen patients who had both hay fever and asthma, but of these, five noted relief of the hay fever but not of the asthma, say Koelsche and his co-workers.<sup>200</sup> Benadryl helped four of twelve asthmatics. Jenkins and his Ann Arbor associates<sup>186</sup> also obtained indifferent results from Benadryl, given intravenously in eight patients. In twenty-three cases of asthma, thirteen of whom had associated allergies, only two of the six patients who obtained excellent results with Benadryl; he obtained better results in other seventy-nine allergic patients with asthma. In 50 mg. doses, Benadryl relieved mild wheezing and dyspnea in five of sixteen of Eyermann's patients;<sup>108</sup> but relief was neither as prompt nor as effective as that from oral 0.03 gm. ephedrine. Severe asthma was not relieved by as much as 100 mg. Benadryl orally. Barnett<sup>225</sup> and his co-workers report poor results in three severe asthmatics. No response occurred in four of eight cases of bronchial asthma, say Blumenthal and Rosenberg;<sup>36</sup> Benadryl relieved symptoms in two cases of cardiac asthma. Cohen and his associates<sup>70</sup>

state: "One asthmatic patient in an acute attack was given 8 mg. intravenously in five minutes. The attack was controlled completely." A Friedlaender<sup>125</sup> reports no benefit in asthma, and S. Friedlaender and Feinberg<sup>126</sup> also found that Benadryl did not help sixteen chronic asthmatics, and Taub<sup>170</sup> confirms this.

Side reactions from Benadryl have been reported by each of the above workers, some more emphatically than others. In addition, Borman's<sup>28</sup> patient, an eighteen-year-old girl took forty capsules (2,000 mg., self-administered) during three days of hay fever and asthma. She became drowsy and irrational, but recovered in forty-eight hours. A three and one-half-year-old boy was given 100 mg. Benadryl for relief of hay fever; six hours later he received 100 mg. again; in twenty minutes the boy was laughing, singing, and irrational, and had involuntary twitching and urination and spastic movements, with recovery next day. [The dosages were obviously too high for these last two patients.] McGavack and his associates<sup>232</sup> also found that Benadryl is a potent sedative, with vertigo, blurred vision, and reduced blood pressure in some of their patients. The drug did help four asthmatics. Three of ten patients who were given 20 to 30 mg. intravenously developed chills, vertigo, headache, low back pain, nausea, drowsiness, and extreme pallor.

Pyribenzamine has also received much attention although it was put out for clinical studies a little later than Benadryl. Mayer and his associates<sup>230</sup> have done a great deal of work with this drug in animals. There is a large margin of safety. In man doses up to 500 mg. per day are usually well tolerated, and the antihistaminic properties of the drug are well proven by its action on intestines, uterus and bronchial muscles of the guinea pig.

Arbesman and his associates,<sup>17</sup> in a study of 495 allergic patients, state that Pyribenzamine relieved or prevented dyspnea and cough in 48 per cent of ninety-eight asthmatics. Side effects occurred but were not serious. The average daily dose was 100 to 400 mg., by mouth. One interesting point: the drug can prevent the onset of asthma from exposure to an allergen, e.g., cat, dog or horse dander, and coffee dust. [This prompts the thought that about 100 mg. doses every four hours might prevent attacks of asthma in those in whom "colds" usually result in asthma.] Friedlaender and Friedlaender<sup>127</sup> report that only two of thirty nonseasonal asthmatics were benefited by this drug, although it was of aid in sixty-nine of 108 cases of allergic rhinitis and in various types of pruritus and hay fever. Feinberg and Friedlaender<sup>110</sup> likewise found the drug has only moderate effectiveness in bronchial asthma.

A committee of the American Academy of Allergy<sup>271</sup> collected statistics from thirteen men, including Arbesman, from various parts of the United States. In a series of 529 cases of bronchial asthma, seasonal and nonseasonal, Pyribenzamine helped 135 (26 per cent). Peculiarly enough, no improvement resulted in 100 cases reported from Florida, and only 17 per cent and 8 per cent in ninety and 209 cases from the New York area and the Midwest, respectively, were improved. There obviously is a great difference of opinion among workers as to what constitutes "improvement."

*Antistine*, another of this group, was given in doses of 100 mg. six times a day by mouth and/or 100 mg. intravenously or intramuscularly. No unfavorable side effects are reported by Kallós, but there was no benefit in twenty-three cases of bronchial asthma.<sup>192</sup> Schindler<sup>302</sup> found only some improvement in six of ten cases of bronchial asthma, using Antistine in patients at the University of Basel. The drug was given orally, intramuscularly and/or intravenously.

*Antergan*, another one, was used by Schwartz and his associates in Norway.<sup>307</sup> The drug failed to help nineteen cases of hay fever, eleven of allergy to flour in bakers, and three cases of aspirin allergy. Side effects were frequent. Frouchtman<sup>130</sup> gave oral Antergan in daily doses of 0.40 to 0.60 gm. for three to six days, with improvement in two cases each of urticaria and allergic rhinitis, but no benefit in two cases of asthma. Undesirable side effects were common.

In addition to the above papers on individual antihistamine drugs, some authors compare the efficiency of one with the others. Curry<sup>51</sup> produced bronchoconstriction, with lessened vital capacity, by injecting histamine in certain asthmatic patients. Intravenous injections of 10 to 30 mg. of Benadryl gave excellent protection against this constriction; Pyribenzamine was tried orally in 50 mg. doses and gave little protection (not tried intravenously). Atropine was fair, but aminophylline, ephedrine and epinephrine were excellent in this respect. Rose and his co-workers,<sup>292</sup> in a study of the effects of Benadryl, Pyribenzamine, Antergan and Neoantergan, conclude: (a) the protection against anaphylactic shock by these four drugs decreases as the amount of the drug is decreased; (b) protection from the four drugs was very similar; (c) findings on the sensitized intestinal strip of the guinea pig bear out the

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lack of difference in protection rendered by Benadryl and Neoantergan in anaphylaxis in the intact animal; (d) against a single lethal dose of histamine these drugs are almost equally effective; (e) observations on the sensitized intestinal strip indicate that the anaphylactic contraction was inhibited by an amount of antihistaminic drug which had no effect on the contraction of the same magnitude due to histamine.

They also state that in a series of patients with asthma, inhalation of these drugs has given much more encouraging results than when the drugs are given by mouth. Feinberg<sup>111</sup> has a long article summarizing the literature on histamine, Benadryl and Pyribenzamine as they affect various allergic conditions. As regards asthma, in his own experience, Benadryl gave definite relief in only 12 per cent of fifty patients, chiefly perennial. Better results followed Pyribenzamine, with improvement in thirty-four (28 per cent of 121 patients; the relief, however, was only moderate, and not nearly as good as that from epinephrine. More over, this drug did not prevent the asthma which frequently accompanies hay fever.

Ratner,<sup>278</sup> whose views are shared by others, concludes that the release of histamine has not yet been proved to be the fundamental factor in anaphylaxis or allergic reactions; hence any therapy based on such a concept must be called into question. The so-called antihistaminic drugs have not proved valuable in eradicating allergic conditions. They do not appear to prevent the entrance of antigen into the circulation and the antigen-antibody reaction. Benadryl and Pyribenzamine do alleviate symptoms in diverse allergic conditions and should have a place along with epinephrine, ephedrine and atropine as excellent antispasmodics. They are not very efficient in asthma and eczema, and they are not cures, some of the public and some physicians notwithstanding. Mayer<sup>231</sup> likewise is not convinced. The mechanism of these drugs is still in doubt, but they do have antihistaminic qualities. Since this is so, further study should unearth the pathogenic role of histamine in numerous manifestations in which such a role has never been suspected or throw overboard other cases of so-called allergy in the origin of which histamine has been falsely accused. [From this survey of the literature on these drugs one can see that they are only slightly effective in asthma when given by mouth. Perhaps intravenous or aerosol methods may give improved results. The role of histamine or H-substance in clinical allergy still remains in doubt.]

Histamine-azoprotein (*Hapamine*) continues to draw a little undeserved attention. Dundy and his co-workers<sup>97</sup> tried it in twenty allergic children, of whom nine had asthma, and in twenty allergic adults, of whom three had infectious asthma. The drug was generally ineffective, both in asthma and in other allergic conditions, and severe local and some general reactions occurred in ten per cent. The authors agree that the histamine theory of allergy has not been proved. M. B. Cohen and Friedman,<sup>71</sup> almost alone, still maintain that the drug is of value in urticaria and in certain cases of bronchial asthma. Systemic reactions, they state, rarely occur, but "large local reactions of this drug led to excellent results in eight, improvement in asthmatics, injections of this drug led to excellent results in eight, improvement in one, and failure in ten [but the authors state that the cases were under observation from four to twelve months, chiefly less than one year, and we all know that any new treatment, even water, can bring temporary relief in certain impressionable asthmatic patients. Furthermore, in seventeen of their nineteen asthmatics they report "etiology unknown." This high percentage may mean that these seventeen are non-reactors, perhaps even "bacterial" asthmatics, but we suggest that complete scratch and intradermal tests should be tried again.]

### ANTIBIOTICS IN TREATMENT OF ASTHMA AND RELATED CONDITIONS

Our statement in the review of the 1945 literature<sup>249</sup> still holds good: "It is therefore difficult at this stage to decide the position of penicillin in the treatment of bronchial asthma. It frequently cures or lessens infectious complications of asthma. Good results seem obtainable both by the usual intermittent injections of penicillin and by the newly developed aerosol technique. But chronic asthma, I am afraid, will still remain after the infection has been removed." Neither the writings of others nor our own added experience in the use of antibiotics changes this opinion.

Penicillin by intermittent injections is widely used in treating the infectious complications of asthma and in other infectious respiratory conditions, e.g., bronchiectasis. The use of sulfonamides in hospital practice seems to have lessened because of possible dangerous reactions, and streptomycin reports are still meager in chest conditions except for its promising results in pulmonary tuberculosis. Leopold<sup>1212</sup> studied eighty-five patients admitted to army hospitals in 1944 and 1945. Infections or intrinsic chronic perennial asthma was present in sixty-two,



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and "extrinsic" asthma with superimposed acute bronchitis or bronchiolitis in the other twenty-three. When the usual allergy treatment failed, penicillin was injected (40,000 units every four hours, with a minimum of 1,680,000 and a maximum of 10,800,000 units in a period of seven to thirty-one days). Results were not encouraging; the symptoms and signs of chronic perennial asthma of the infectious type were not cleared permanently; temporary and partial improvement occurred in twenty (32 per cent). The signs of asthma were not completely cured in any case, and seventy-six (89 per cent) of the total of eighty-five cases were not improved. The volume of sputum was decreased and remained so after treatment in twenty-one (33 per cent of the infectious group; and six (26 per cent) of the patients with superimposed bronchitis also had less sputum. There was practically no change in organisms cultured from the sputum of sixty-nine patients (81 per cent).

Miller<sup>240</sup> gave penicillin intramuscularly to twenty-nine "intrinsic" asthmatics. It is not a panacea for this type of asthma, but it is effective in a small but worthwhile proportion of infectious cases. All cases were in the hospital, and the control of any intrinsic factors was maintained. The dosage was 12,500 to 25,000 units every three hours, with an average total dose of 1,300,000. Excellent response occurred in eleven of the twenty-nine patients, improvement in eleven, no relief in seven. Relapse occurred in four of the "excellent" group, and in six of the "improved," when penicillin was stopped.

Kaufman's patient<sup>193</sup> had severe infectious bronchial asthma, and was relieved by injections of 10,000 units penicillin every two hours, with a total of 1,900,000. Wheezing did not return for two months. Bauman and his associates<sup>26</sup> treated twelve adults and twenty-four children ("bacterial" asthmas) with three penicillin tablets (20,000 units each) orally, every three hours for three days, day and night, with a total of 1,440,000 units. Blood levels were satisfactory (0.03) in all but three cases. Pneumococci were eliminated from nasal cultures, but staphylococci were not much affected. Clinical results were good for six weeks to four months in 71 per cent of thirty-six cases.

Boyd and Dorrance<sup>43</sup> found that some of the sulfa drugs, especially sulfadiazene, have an expectorant action, with an increased rate of output in the bronchial secretion. They worked with animals but suggest that sputum in man will also contain the drug, if administered.

Inhalation penicillin therapy has become very popular. As an editorial in *ANNALS* or *ALLERGY* states,<sup>100</sup> priority in this field belongs to Abramson; he worked with aerosol penicillin and with other aerosol projects while with the Chemical Warfare Service, and was awarded the Legion of Merit. In an excellent paper,<sup>2</sup> Abramson discusses the principles and practice of aerosol therapy of the lungs and bronchi. He tells how the work was initiated; gives definitions of aerosol, atomization, nebulization, vaporization, and aerosolization; describes in detail large particle atomization and small particle nebulization; states that rebreathing is inefficient; describes simple apparatus and discusses its use with epinephrine, penicillin, streptomycin, sulfonamides, and hydrogen peroxide. For nebulization he prefers the De Vilbiss 40 or the Vaponefrin. He adds 25 per cent glycerol to 1:100 epinephrine to stabilize the solution.

Hydrogen peroxide solution, with 10 per cent glycerol in physiologic saline, is readily nebulized without loss of stability, whether used as hydrogen peroxide directly or as urea peroxide. There is no appreciable irritation. This aerosol was used in cases of asthma, asthma with infectious bronchitis, bronchiectasis and lung abscess, and was alternated with penicillin aerosol. Both Gram-positive and Gram-negative organisms can be destroyed by this combination.

Barach and his associates<sup>22</sup> have also been active in inhalation therapy. In the treatment of severe asthma, they discuss inhalation of oxygen and helium and Demerol by injection. They advise inhalation with penicillin in moderate dosage for one to three months. Inhalation of sodium sulfathiazole (1 to 5 per cent) is helpful in bronchopulmonary infection, but the authors prefer penicillin because of its greater bacteriostatic power against streptococci and staphylococci, and the fact that its bacteriostatic action is not inhibited by purulent secretions or P-aminobenzoic acid. They use 50,000 units penicillin in 1 c.c. of normal saline, with inhalations every three hours; this gives satisfactory blood levels. [Abramson points out that inhalation therapy helps by its direct action on the respiratory tract; he is not too much concerned about blood levels.]

In a series of eighty-six courses of treatment in fifty-one patients with chronic hypertrophic pulmonary emphysema Barach, et al, felt that improvement due to penicillin aerosol was marked in twenty, moderate in nineteen, slight in twenty-five, and absent in twenty-two. Other methods of treatment (physiologic therapy) gave



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markedly good results in nine, moderate in thirty-six, slight in twenty-three, and none in eighteen. Of the sixty-six improved cases, thirty-one seemed more influenced by physiologic therapy, twenty-seven by penicillin, and eight by both equally.

Segal and his associates<sup>307</sup> helped many patients, some dramatically, by giving penicillin aerosol to eighty-five patients with bacterial pneumonia, suppurative bronchitis, bronchiectasis, lung abscess, infective bronchial asthma, infective laryngotracheobronchial edema, and emphysema. Generally, 25,000 units of penicillin were dissolved in normal saline and inhaled at three-hour intervals. A nebulizer was used which gave a fine mist. Streptomycin can be combined with penicillin in an aerosol. In a later report, their results in twenty-two cases of infective bronchial asthma were disappointing, although striking improvement was occasionally observed. Their results in bronchopulmonary infectious conditions continued to be good. Recurrences were few (bronchospasm, two instances of urticaria, and four of stomatitis, in 118 patients). Segal also has a long article on "Progress in Inhalation Therapy," in which he reviews the literature. Strangely enough, he does not mention Abramson's studies which preceded those of Bryson and others.

Prigal and his co-workers<sup>266</sup> favor the use of a combined steam generator and aerosolizer. They also use other methods, e.g., the tent, which is best for infants and children. The steam generator can be used in the office or at home. It is inexpensive and safe, and any aerosol can be used.

Finke, in seventy-two patients with respiratory disease,<sup>112</sup> found no benefit from penicillin aerosol in two cases of intrinsic asthma; in ten patients with "mixed allergic-infectious" asthma the response was good by combined aerosol and control of allergic manifestations. Fishman<sup>116</sup> obtained good results in fifteen cases of infectious complications of asthma by using an ordinary nose and throat atomizer and 100,000 units of sodium penicillin solution in 50 cc of distilled water 1 cc. of this solution (pH 6) is inhaled as one dose every three hours. This is confirmed by Morse.<sup>217</sup> Hamburger and his associates,<sup>133</sup> by measurements of voluntary apnea and the speed of expired air, conclude that the "treatment of this affection" gives results superior to the various other types of treatment of asthma by aerosols. [We must dissent from this view.] Toch and Steele<sup>313</sup> obtained good results in three elderly asthmatic patients who also had infectious processes in the lungs, and in one asthmatic who also had auricular fibrillation and congestive heart failure. They point out that penicillin, by whatever route, cannot be expected to cure "long-standing chronic bronchitis or chronic bronchiectasis, or asthmatic bronchitis with emphysema and fibrosis of the lungs or chronic sinusitis accompanied by polypoid and thickened lining membrane."

Southwell,<sup>321</sup> in a study of forty-three patients with bronchiectasis, bronchitis, or asthma, gave penicillin inhalations on an out-patient basis; a course of treatment consisted of 1,000,000 units given in inhalations of 100,000 units two to three times daily. In seventeen cases of chronic bronchitic asthma, one cleared entirely and all but three were improved, but there was no improvement in four cases of allergic asthma. Englesher<sup>105</sup> used 20,000 units every three to four hours for two to four weeks in seventy-four chronic asthmatics; only 15 per cent were slightly benefited, and 85 per cent received no benefit. In many of these patients parental penicillin was also used without results. Seltzer<sup>310</sup> likes the DeVilbiss 40 nebulizer, and when it becomes obstructed he washes it through a small hypodermic needle attached to an ordinary syringe.

Many other papers discuss aerosol penicillin, especially as used in the treatment of bronchopulmonary infection. In bronchiectasis not suitable for lobectomy, Siltzbach<sup>316</sup> was able to lessen the volume of sputum in ten of thirteen cases, along with a lessening of infection and the odor of the sputum. Bobrowitz and his co-workers<sup>37</sup> treated sixteen patients with severe bronchiectasis with a total dosage of 550,000 to more than 5,500,000 units over four to 115 days. Best results were obtained when the penicillin was instilled in the trachea; less effective was inhalation; least effective injections. Results were excellent during administration, i.e., reduction in amount, odor and pus in sputum, and elimination of most bacteria, and marked symptomatic relief. Treatment must be continued indefinitely as relapse occurs on discontinuance.

Fullerton and Shane<sup>132</sup> used penicillin aerosol in fourteen patients with bronchopulmonary disease. Virus pneumonia was not aided, but good response occurred in four cases of lobar pneumonia and in lung abscess. There was no alleviation of the asthmatic state in five patients. In nine cases of chronic bronchiectasis in which penicillin aerosol failed, Olsen<sup>257</sup> tried streptomycin; this removed Gram-negative bacteria and lessened the volume of sputum. Olsen advises combined penicillin and streptomycin aerosol preoperatively for pulmonary resection and as a temporary

measure in non-surgical bronchiectasis. Hanks<sup>152</sup> used small amounts of penicillin in aerosol, but obtained good results in thirty-four patients with respiratory infections, including virus pneumonia. Pyle<sup>270</sup> was able to eliminate penicillin-sensitive bacteria from the sputum of three patients with bronchial asthma and bronchiectasis, but the aerosol did not change the underlying pathologic condition.

Humphrey and Jones<sup>173</sup> studied various pulmonary diseases. Penicillin by inhalation gave excellent results in acute and subacute infections, but results with chronic infections were much less evident; of the eighty cases, forty-six were much improved, seventeen improved, and seventeen not improved. Levine<sup>214</sup> studied forty-two patients with chronic bronchiectasis in whom all previous treatment had failed, including parenteral penicillin. Penicillin aerosol was given every three hours for three to four weeks in doses of 1,000 to 20,000 units per c.c. Complete relief of symptoms occurred in nineteen, improvement in fourteen, and no relief in eight, but Levine, as do all others, points out that symptoms and bacteria return when the aerosol is stopped. In four asthmatic patients Hurst<sup>175</sup> obtained improvement by aerosol in two, one of whom developed angioneurotic edema on the ninth day.

Pulmonary instillation of a mixture of penicillin and iodized oil has been tried in bronchiectasis and lung abscess. Results are still uncertain.<sup>101</sup>

Thus we see that the above writers are fairly well agreed that inhalation of penicillin is excellent in treating bronchopulmonary diseases, especially if acute. It is less effective and gives only temporary benefit in bronchiectasis; it is useful in the infectious complications of asthma, but of little or no benefit to the underlying asthma. Our own experience in our asthma rooms at Wesley Memorial Hospital, Chicago, in a large series of cases, confirms these findings. We have used penicillin (and streptomycin in a few cases) both by injection and by inhalation; sometimes we have used both at the same time. The underlying asthma persists in many cases, but we are pleased with the method because the fever, high sedimentation rate, and leukocytosis usually clear, and the patients feel better. Our results in bronchiectasis have been mediocre, except when lobectomy is possible.

*(To be concluded in March-April issue. Complete list of references will appear with final installment.)*

## PHYSIOLOGY OF THE LUNGS AND THE ASTHMATIC STATE

*(Continued from Page 63)*

An attempt was made to produce congestion of the lung in the living animal and to determine its effect on the distensibility of the lung. This was accomplished by placing a rubber-tipped clamp on two or three of the pulmonary vein and their entrance to the left atrium. This clamp acted very much like a severe mitral stenosis with pulmonary congestion. The volume-pressure curves obtained with the pulmonary veins occluded showed a decrease in distensibility of the lung.

WANTED—Resident and Fellows in Allergy. Facilities for clinical work and research available. Period of training of one year or longer with compensation. GRAHAM-THOMAS CLINIC, 201 West Franklin Street, Richmond 20, Virginia.

# \* *In Memoriam* \*

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## PHILIPP SCHONWALD, M.D., F.A.C.A.

Dr. Philipp Schonwald, physician who attained world acclaim for discovery of a Penicillin substitute, passed away at his home in Seattle, Washington, in December, 1947. Dr. Schonwald was born and educated in Vienna. His 43-year medical career began in 1904 with his graduation from the University of Vienna Medical School. A long-felt desire to come to the United States prompted him to leave a post as chief of the medical staff of a large sanitarium near Vienna. He went to Seattle in 1921 as an established chest specialist. He was a pioneer in thorocoplasty, pneumothorax and intrapleural pneumolysis having performed many of these operations for tuberculosis, in their early development. He realized that many non-tuberculosis chest diseases were of an allergic nature and this led to his pioneer studies in allergy and related fields which he carried on to his last day. Dr. Schonwald was one of the original investigators on the allergic factor of soil bacteria and an early investigator on allergies traceable to mold spores. A great deal of his latter work was carried on while he was a wheel chair invalid. Six years ago he suffered a stroke which caused a left hemiplegia. He continued to publish many articles on allergy, molds and fungi, and their clinical application. A paper describing his search for an antibiotic to attack bacteria in the human colon will be published soon. He was an active member and contributor to scientific allergy as well as tuberculosis organizations and journals.

During twenty-six years' practice in Seattle Dr. Schonwald served on the staffs of the Riverton, Morningside and Swedish hospitals. He was a member of the American Medical Association, King County and Washington State Medical Societies, the American Trudeau Society and the International Correspondence Society of Allergists. He was a Fellow of the American College of Chest Physicians, American Academy of Allergy, American College of Tuberculosis Physicians, American College of Physicians, the International Association of Allergists and the American College of Allergists.

The College deeply regrets the loss of such a loyal friend and the members extend their most sincere sympathies to the family.

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## RESTRICTED DIET FOR DETERMINATION OF SUSPECTED FOOD ALLERGY. First Edition. St. Louis 2, Missouri: Ralston Purina Company, 1946.

This is a diet sheet compiled by Miss Elspeth Bennett, Manager, Nutrition Service, Ralston Purina Company, in collaboration with a panel of allergists. It is intended for use when the physician wishes to apply dietary means in the difficult task of tracking down offending foods. Though no one diet can be applicable to all such cases, this one, made up as it is of a carefully selected list of foods to which few persons are sensitive should find wide application. Detailed information clearly given simplifies the problem of such a restricted diet for both physician and patient.

Menu guides and tested recipes make possible a variety of appetizing meals despite the limited number of foods. Timely buying information is also given. This new diet should prove a valuable addition to the wheat-free, egg-free, milk-free and wheat-egg-milk-free diet sheets that the Ralston Purina Company has made available to physicians for many years. As with these other diets, this new one is available to physicians in pads of twenty-five diet sheets.

# News Items

## NEWS OF SOCIETIES

The Ohio Valley Allergy Society will hold its next meeting at Springfield, Ohio, May 22, 1948. Dr. Armand Cohen of Louisville, Kentucky is Chairman and Dr. D. J. Parsons of Springfield, Ohio, is the Secretary-Treasurer.

\* \* \*

At the annual meeting of the Los Angeles Society of Allergy (a Section of the Los Angeles County Medical Association), the following officers were elected for 1948:

President—Willard S. Small, M.D., Pasadena

Vice President—Hyman Miller, M.D.

Secretary-Treasurer—Frank G. Crandall, Jr., M.D.

George Piness, M.D., who was the president during 1947, was elected to the Executive Council for 1948.

These officers were installed at the January meeting of the Society.

\* \* \*

At the November meeting of the Pittsburgh Allergy Society, the following officers were elected and committees appointed:

President—Lester Bartlett, M.D.

Secretary-Treasurer—Mayer A. Green, M.D.

*Membership Committee*—A. R. McCormick, M.D., Chairman; J. Gordan, M.D., and W. Ruehl, M.D.

*Program Committee*—Sylvia Wechsler, M.D., Chairman; R. Hamilton, M.D., and A. H. Neidorff, M.D.

*Pollen Commission*—E. P. Claus, Ph.D., Chairman; J. Mansmann, M.D.; P. Blank, M.D., and L. Crip, M.D.

## CENTRAL PENNSYLVANIA ALLERGY SOCIETY

The spring meeting of the Central Pennsylvania Allergy Society will be held in York, Pennsylvania, at the Yorkshire Hotel on April 1, 1948. The luncheon and business meeting will take place between 11:00 A.M. and 1:00 P.M., and the scientific session will follow. The banquet for members and their wives will be held in the evening, with Lt. Governor Strickler of Pennsylvania as the principal speaker. All members are urged to attend and other physicians interested are welcome.

### Program

- 1:25 Address of Welcome—CHARLES FACKLER, M.D., President of York County Medical Society.
- 1:30 "General Concepts of Allergy"—A. HARVEY SIMMONS, M.D.
- 1:45 "Treatment of Bronchial Asthma"—ETHAN ALLAN BROWN, M.D.
- 2:30 "The Place of Irradiation of the Nasopharynx in the Treatment of Selected Cases of Asthmatic Bronchitis in Children."—JOHN E. BORDLEY, M.D.
- 3:00 *Intermission*
- 3:15 "Cytology of Nasal Secretions with Special Reference to Allergic Diseases."—M. VALENTINE MILLER, M.D.
- 4:00 "Headache from the Allergic Point of View."—FRANK F. FURSTENBERG, M.D.
- 4:30 "Mycotic Infection of Bronchi and Lungs—Their Relationship to Allergy."—LEO H. COLLINS, M.D.
- 5:00 "Role of Anti-histaminics in Allergy."—MERLE MILLER, M.D.

## SUSTAINING MEMBERSHIP

In the September-October issue of the ANNALS OF ALLERGY, an announcement was made in these columns of the establishment of Sustaining Membership by the College. This has been the custom of a number of scientific organizations for some time, such as is done by the American Society of Bacteriologists. It is logical that these firms associated with the allergists, both in a business and a co-operative way, be recognized as Sustaining Members. All of these members will be listed in each issue of the ANNALS and will receive subscriptions to the ANNALS. We are very pleased to introduce in this issue the first list of Sustaining Members of the American College of Allergists (Page xii).

## TWENTIETH ANNIVERSARY YEAR OF HAROFÉ HAIVRI

The attention of the medical profession is directed to the appearance of the Fall issue of *Harofé Haivri* (The Hebrew Medical Journal), a semi-annual bilingual publication edited by Moses Einhorn, M.D.

In the medical section, the following subjects are offered: "The Importance of the Rh Factor in Clinical Medicine" by Philip Levine, M.D., and Pharmacology and Toxicology of Streptomycin" by Ernst Pick, M.D.

The section on Palestine and Health contains the following articles: "The Contribution of Bacteriologists for the Control of Infectious Diseases in Palestine" by L. Olitski, M.D., of the Hebrew University; "The Present Status of Tuberculosis in Palestine" by A. Wolowelsky, M.D., and "Plastic Surgery in Palestine" by Ernst Wodak, M.D.

Under the heading of Historical Medicine Dr. Leon Nemoy of Yale University writes on the great philosopher and physician of the 13th century—Ibn Kammuna. Dr. Yom-Tov Levinsky discusses in his article on Folklore Medicine, the legends surrounding frogs and spiders as healing agents.

The original articles are summarized in English to make them available to those who are unable to read Hebrew. The editorial office of *The Hebrew Medical Journal*, 983 Park Avenue, New York 28, N. Y., will be glad to furnish any further information desired.

## NATIONAL BLOOD PROGRAM

Mr. Louis C. Boochever, Director of Public Relations of the American National Red Cross, National Headquarters, Washington 13, D. C., announces:

"The American Red Cross is undertaking one of the most far-reaching peacetime projects in its history—a National Blood Program which promises to be a valuable adjunct to medical science in protecting the health of the American people. The Program will provide whole blood and its derivatives to the entire nation without charge for the products.

"The Program has been approved in principle by officials of the American Medical Association, American Hospital Association, Veterans Administration, Army, Navy, United States Public Health Service, the American Health Association, and others in medical and scientific fields."

The American National Red Cross is also prepared to offer to members of the College represented by the ANNALS OF ALLERGY, the services of special writers in the preparation of articles or editorial material. The organization will be glad to provide information and background material for the use of the ANNALS' staff writers who may be interested in preparing articles on the National Blood Program. The National Headquarters will also be glad to arrange to take special pictures in addition to making available glossy prints from their files. They will gladly furnish anyone interested with a "Fact Sheet" outlining the Program, setting forth the reasons for their decision for a National Blood Program, what the National Blood Program will be and what it will provide.

(Continued on Page 98)



# BRONCHIAL ASTHMA.. HAY FEVER - URTICARIA

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Write for descriptive literature and professional samples.



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## NEWS ITEMS

*(Continued from Page 96)*

The Program includes the providing of blood and blood derivatives, without charge, to patients, physicians, and hospitals. The only charge ever made to the patient is for professional services in administering the material. In addition to whole blood plasma, the National Blood Program will provide other blood derivatives of proved value, such as: Serum Albumin, Immune Serum Globulin, Antihemophilic Globulin, Blood Grouping Serum, Fibrin Films and Thrombin, Red Cell Suspensions, and Red Cell Paste and Powder. Any blood derivatives that continued research may find useful in medicine will be made available through the Program.

\* \* \*

The U. S. Army Medical Corps now has a number of excellent positions which can be filled by physicians who have completed their formal board requirements (residence phase) but who need one or two years of practice limited to their specialty.

There are 24 openings for Internal Medicine; 15 for Neuropsychiatry; 14 for Obstetrics and Gynecology; 11 for Radiology; 10 for Pediatrics; 7 in Anesthesia; 5 in Orthopedic Surgery, et cetera. Positions will be offered in eleven station hospitals in Germany and two in Austria.

These requirements provide excellent facilities and equipment, and a wealth of clinical material. The applicant may avail himself of this training for periods of one, two or three years. Selected applicants who hold reserve commissions in the Medical Corps, will usually be recalled to active duty in the highest grade attained prior to release from previous active service.

Eligible physicians are invited to communicate with The Surgeon General, U. S. Army, Washington 25, D. C., for further information.

\* \* \*

Announcement that Dr. J. P. Gray has joined the staff of Parke, Davis & Company in the capacity of Medical Consultant to the Sales and Promotion Division has been made by Harry J. Loynd, vice president of the Company.

Dr. Gray comes to Parke, Davis with an exceptional medical background. A graduate of Johns Hopkins University with an M.D. degree, and of the Harvard School of Public Health with an M.P.H., he served in public health work for many years, including posts with the United States Marine Hospital in New Orleans, the state of California and the city of San Francisco, and the Michigan Community Health Project of the W. K. Kellogg Foundation. He also is an educator, having lectured in public health at the University of California, served as dean of the School of Medicine of the Medical College of Virginia in Richmond, and also as dean of the School of Medicine, University of Oklahoma, and superintendent of the University hospitals.

\* \* \*

Amino acids in tablet form have been introduced by the Maltine Company, of New York City, a member firm of the American Pharmaceutical Manufacturers' Association. The new product, known as Nitramac Tablets, has overcome the taste problem by approaching it from a new direction, according to the Company. The tablet is not a disc or wafer to be chewed but is a true tablet which is swallowed whole. In this form the amino acids are carried past the taste buds by a swallow of water before they can excite a taste response.

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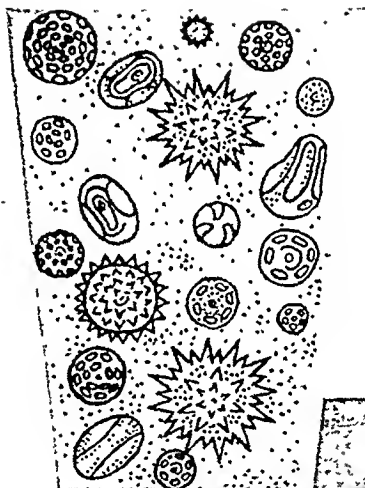
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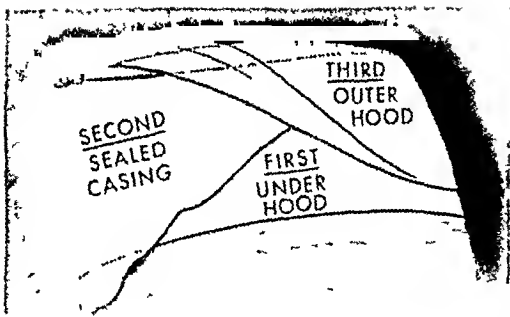
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